

## SPECIFICATION

### Dihydrodiaryloxazepine derivative and pharmaceutical composition containing the same

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#### Background of the Invention

The present invention relates to 5,11-dihydrodiaryl[b,e][1,4]oxazepine derivatives, antagonistic to calcium channels and useful for treating or preventing functional diseases of gastrointestinal tracts, in particular, irritable bowel syndrome, and stereoisomers thereof, pharmacologically acceptable salts thereof or hydrates thereof and also pharmaceutical compositions containing any of them as the active ingredient.

The present invention also relates to intermediates for producing the new 5,11-dihydrodiaryl[b,e][1,4]oxazepine derivatives.

It is disclosed in, for example, European Patent No. 0404359 that the 5,11-dihydrodibenzo[b,e][1,4]thiazepine derivatives are useful as antagonists to calcium channels, which are selective for the gastrointestinal tracts. Quinn, P. et al. [Brit. H. Pharmacol., 1994, 112 (Suppl.), Abst. P. 573] and Wallis, R. M. et al. [Brit. J. Pharmacol., 1994, 112 (Suppl.), Abst. P. 574] disclosed that (S)-5-[[1-(4-methoxyphenyl)ethyl]pyrrolidin-2-ylmethyl]-5,11-dihydrodibenzo[b,e]-[1,4]thiazepine maleate has the same effect as the one described above. However, the activity and selectivity of those compounds for the gastrointestinal tracts are not yet satisfactory and another defect of them is that they have an anticholinergic effect that causes side effects such as

a thirst and mydriasis. Further, International Patent Nos. 9733885A1 and 9912925A1 disclose 5-(2-pyrrodinylmethyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine derivatives as agents for improving the movement of the digestive tracts. In addition, International Patent No. 0040570A1 discloses 5-alkyl-5,11-dihydrodibenzo[b,e][1,4]oxazepine derivatives as agents for improving the movement of the digestive tracts. However, the activity and selectivity of those compounds for the gastrointestinal tracts is not yet satisfactory and they have not yet been used as drugs.

10 As the social environment is being complicated recently, many people are under great stress and patients suffering from irritable bowel syndrome and having abnormal bowel movement and abdominal pain as the cardinal symptoms are increasing in number. Drugs used for ameliorating such diseases are, for example, a cholinergic blocking drug, laxatives, antidiarrheal drug, drug for intestinal disorders, mucosal paralyzant, agent for regulating gastrointestinal motor functions, agent for regulating autonomic nerves, herb medicine, antianxiety drug, antidepressant drug, sleeping pill, antipsychotic drug, serotonin receptor antagonist and serotonin receptor agonist. However, the clinical effects of those drugs are yet insufficient and they are not always satisfactory because of the side effects. Under these circumstances, the development of a new type of drugs having an excellent effect of improving functional gastrointestinal diseases and free of side effects is desired.

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Disclosure of the Invention

An object of the present invention is to provide new compounds having excellent effect of improving functional gastrointestinal diseases.

Another object of the present invention is to provide a pharmaceutical composition containing the new compound(s).

5 Still another object of the present invention is to provide intermediates for producing the new compounds.

Antagonists to calcium channels are considered to be effective on diseases caused by an abnormally accelerated contraction of the intestinal tracts such as irritable intestinal syndrome because they have  
10 an effect of controlling the contraction of smooth muscles. In fact, it was reported that antagonists to calcium channels such as Nicardipine and Verapamil are effective on irritable intestinal syndrome [Am. J. Gastroenterol., 80, 317 (1985), Gut, 28, 1609 (1987), J. Clin. Psychiatry, 48, 388 (1987), Pharmacol. Ther., 60, 121 (1993)]. However, these  
15 antagonists to calcium channels are scarcely clinically used at present because of the main effect of them on the cardiovascular system. Under those circumstances, the inventors made intensive investigations for the purpose of developing antagonists to calcium channels selectively effective on intestinal tracts and having only a low toxicity or, in other  
20 words, inert to the cardiovascular system, as therapeutic agents for functional gastrointestinal diseases, particularly irritable bowel syndrome. As a result, the inventors have found that the calcium antagonistic effect of 5,11-dihydrodiaryl[b,e][1,4]oxazepine on the intestinal tracts is improved and also the selectivity for the calcium  
25 antagonistic effect on blood vessels is also improved by introducing a halogen atom into at least one of 1-, 2-, 3-, 4-, 6-, 7-, 8- and 9-positions

thereof and/or by introducing a cyclic amino group having a specified structure on a terminal aromatic ring.

Namely, the inventors have found that compounds of general formula [I] given below have the antagonistic activity to calcium channels,  
5 which is selective for the intestinal tracts and, therefore, they are effective as agents for improving functional gastrointestinal diseases. The present invention has been attained on the basis of this finding.

The compounds of the present invention are useful as remedies for functional gastrointestinal diseases including gastrointestinal motor  
10 function diseases, such as irritable bowel syndrome, rumination syndrome, globus syndrome, functional heart burn, functional chest pain of presumed esophageal origin, functional gastrointestinal disorder, functional dysphagia, functional vomiting, deglutition disorder, aerophagia, functional constipation, functional abdominal bloating,  
15 functional abdominal pain syndrome, functional diarrhea, sphincter of Oddi's dysfunction, gallbladder dysfunction, levator ani syndrome, functional fecal incontinence, pelvic floor dyssynergia proctalgia fugax and pediatric gastrointestinal function disorders (such as infant regurgitation syndrome, infant rumination syndrome, cyclic vomiting  
20 syndrome, functional gastrointestinal disorders, irritable bowel syndrome, functional abdominal pain, paroxysmal abdominal pain, aerophagia, functional diarrhea, infant dyschezia, functional constipation, functional fecal retention and functional non-retentive fecal soiling). The compounds of the present invention are particularly useful for the  
25 treatment of irritable bowel syndrome.

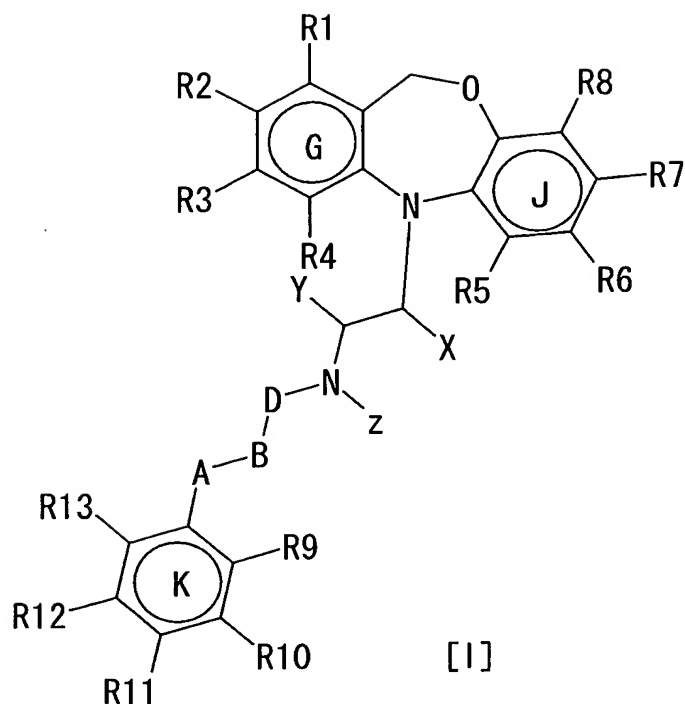
The compounds of the present invention are also useful for the



treatment of diseases with pathology similar to that of functional gastrointestinal diseases [neuropathies such as anxiety disorders (panic disorder and generalized anxiety disorder), somatoform disorder, dissociated disorder and neuroses such as emotional disorder, bulimia, nervous anorexia, somniphobia, diabetic gastrointestinal disease, etc.] and gastrointestinal symptoms after surgical operation of the abdomen.

The compounds of the present invention are usable for the treatment of the above-described diseases either alone or in combination with a cholinergic blocking drug, laxatives, antidiarrheal drug, drug for intestinal disorders, mucosal paralyzant, agent for regulating gastrointestinal motor functions, agent for regulating autonomic nerves, herb medicine, antianxiety drug, antidepressant drug, sleeping pill, antipsychotic drug, serotonin receptor antagonist and serotonin receptor agonist. The compounds of the present invention are expected not only to have the excellent pharmacological effect but also to be metabolically stable.

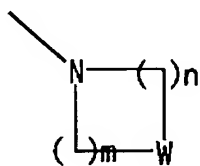
Namely, the present invention relates to 5,11-dihydrodiaryl[b,e][1,4]oxazepine derivatives represented by the following general formula [I], stereoisomers thereof, pharmacologically acceptable salts thereof, hydrates or solvates thereof and pharmaceutical compositions containing them as the active ingredient:



wherein rings G, J and K each represent benzene ring or a nitrogen-containing aromatic ring;  $R^1$  to  $R^8$  may be the same or different from one another and they each represent a halogen atom or a hydrogen atom,  $R^9$  to  $R^{13}$  may be the same or different from one another and they each represent a hydrogen atom, a halogen atom, cyano group, hydroxyl group, a lower alkyl group, a lower alkoxy group, amino group or a lower dialkylamino group or a lower acylated derivative of such a group, a lower dialkylamino group or a cycloalkylamino group, or  $R^9$  and  $R^{10}$  or  $R^{10}$  and  $R^{11}$  together form  $-O(CH_2)_nO-$  group wherein  $n$  is 1, 2 or 3; A represents  $CH_2$ ,  $CHOH$ ,  $CO$  or  $O$ ; B represents  $CH_2$ ,  $CHOH$  or  $CO$ ; or A-B represents  $CH=CH$ , D represents  $CH_2$ ,  $CH_2-CH_2$  or  $CH_2-CH_2-CH_2$  or B-D represents  $CH_2$ ; X and Z are bonded together to form  $CH_2-CH_2$  or  $CH_2-CH_2-CH_2$  and, in this case, Y represents a hydrogen atom; or Y and Z are bonded together to form  $CH_2-CH_2-CH_2$  or  $CH_2-CH_2-CH_2-CH_2$  and, in this case, X

represents a hydrogen atom; and when X and Z, and Y and Z are not bonded together, X and Y each represent a hydrogen atom and Z represents a lower alkyl group;

provided that when any of  $R^9$  to  $R^{13}$  represents a cyclic amino group of the following formula [E],  $R^1$  to  $R^8$  may be a halogen atom or hydrogen atom but when none of  $R^9$  to  $R^{13}$  is a cyclic amino group of formula [E], one or two of  $R^1$  to  $R^8$  represent a halogen atom and the others represent a hydrogen atom:

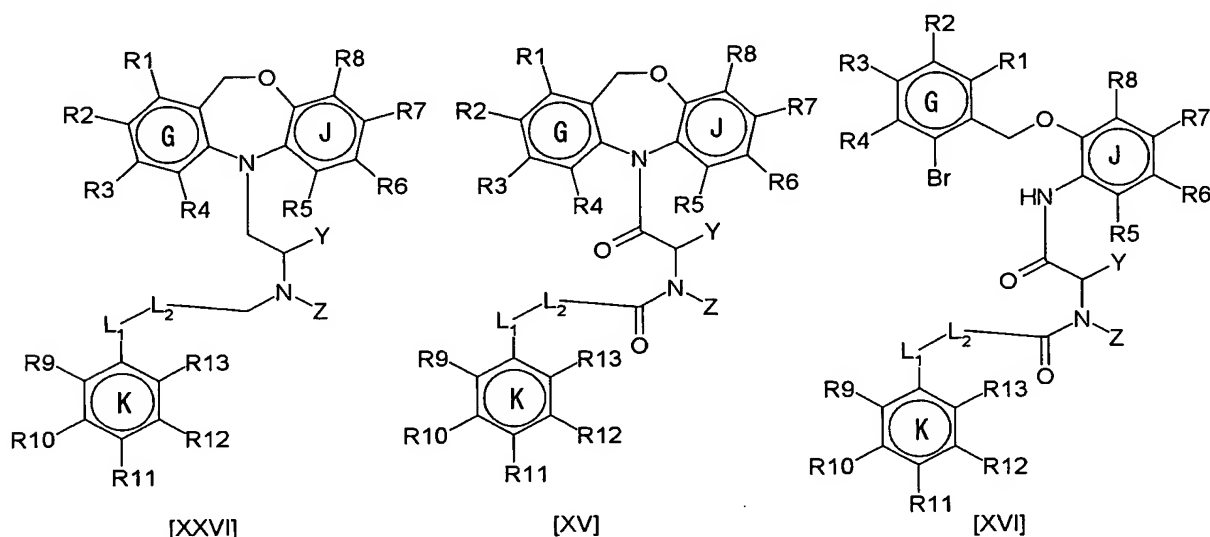


[E]

wherein n and m each represent 1 or 2, and W represents carbon atom, or nitrogen which may be substituted with a lower alkyl group, or oxygen, or sulfur atom.

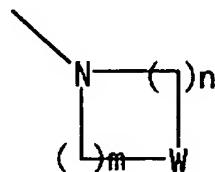
In the 5,11-dihydrodiaryl[b,e][1,4]oxazepine derivatives, compounds of above general formula [I] wherein X represents a hydrogen atom and Y and Z are bonded together to form  $\text{CH}_2\text{-CH}_2\text{-CH}_2$  or  $\text{CH}_2\text{.CH}_2\text{.CH}_2\text{-CH}_2$  or X and Y each represent a hydrogen atom and Z represents a lower alkyl group are represented by general formula [XXVI]. The inventors have also found that those compounds [XXVI] can be produced by the intramolecular arylation of a corresponding amide derivative of general formula [XVI] or a salt thereof to obtain a 5,11-dihydrodiaryl[b,e][1,4]oxazepine derivative of general formula [XV] or a salt thereof followed by the reduction of the derivative or the salt.

Namely, the present invention also relates to compounds of general formulae [XV] and [XVI], which are important intermediates for producing the compounds of general formula [XXVI], among the compounds of general formula [I], as well as stereoisomers and salts thereof:



wherein rings G, J and K each represent benzene ring or a nitrogen-containing aromatic ring; R<sup>1</sup> to R<sup>8</sup> may be the same or different from one another and they each represent a halogen atom or hydrogen atom, R<sup>9</sup> to R<sup>13</sup> may be the same or different from one another and they each represent a hydrogen atom, a halogen atom, cyano group, hydroxyl group, a lower alkyl group, a lower alkoxyl group, amino group or a lower dialkylamino group or a cycloalkylamino group, or R<sup>9</sup> and R<sup>10</sup> or R<sup>10</sup> and R<sup>11</sup> together form -O(CH<sub>2</sub>)<sub>n</sub>O- group wherein n is 1, 2 or 3; L<sub>1</sub> represents CH<sub>2</sub>, CHOH or O; L<sub>2</sub> represents CH<sub>2</sub>, CHOH, CH<sub>2</sub>-CH<sub>2</sub>, CHOH-CH<sub>2</sub>, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub> or CHOH-CH<sub>2</sub>-CH<sub>2</sub>; or L<sub>1</sub> and L<sub>2</sub> are bonded together to form

CH<sub>2</sub>, CHOH or CH=CH, Y and Z are bonded together to form CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub> or CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub> or when Y and Z are not bonded together, Y represents a hydrogen atom and Z represents a lower alkyl group; provided that when any of R<sup>9</sup> to R<sup>13</sup> represents a cyclic amino group of the following formula [E], R<sup>1</sup> to R<sup>8</sup> may be a halogen atom or hydrogen atom but when none of R<sup>9</sup> to R<sup>13</sup> is a cyclic amino group of formula [E], one or two of R<sup>1</sup> to R<sup>8</sup> represent a halogen atom and the others represent a hydrogen atom:



[E]

wherein n and m each represent 1 or 2, and W represents carbon atom, or nitrogen which may be substituted with a lower alkyl group, or oxygen, or sulfur atom.

#### Best Mode for Carrying Out the Invention

The nitrogen-containing aromatic rings G, J and K in the above general formula [I] are desirably compounds having a 6-membered ring such as pyridine ring, pyrimidine ring, pyrazine ring or pyridazine ring with the proviso that nitrogen atom constituting an aromatic ring cannot be placed on the oxazepine ring, that when any of R<sup>1</sup> to R<sup>8</sup> is a halogen atom, this halogen atom is not bonded to the nitrogen atom in the aromatic ring and that, in ring K, the nitrogen atom constituting the

aromatic ring is not bonded with A and the nitrogen atom is not bonded with any substituent.

As for rings G, J and K, the following five cases (i) to (v) are preferred: (i) both rings G and J are benzene rings, (ii) one of rings G and J is pyridine ring and the other is benzene ring, (iii) ring K is benzene ring and rings G and J are as described in (i) or (ii), (iv) ring K is pyridine ring, pyrimidine ring, pyrazine ring or pyridazine ring and rings G and J are as described in (i) or (ii), and (v) rings G, J and K are all benzene rings. In general formulae [XV] and [XVI], the above-described five cases (i) to (v) are preferred.

The halogen atoms as  $R^1$  to  $R^8$  in the above general formula may be fluorine atom, chlorine atom, bromine atom, etc. In them, fluorine atom or chlorine atom is preferred. It is more desirable that one of  $R^2$ ,  $R^3$ ,  $R^6$  and  $R^7$  in  $R^1$  to  $R^8$  is fluorine atom or chlorine atom and the others are each a hydrogen atom. In  $R^9$  to  $R^{13}$ , the halogen atoms include fluorine atom, chlorine atom, bromine atom, etc., and the lower alkyl groups include those having 1 to 5 carbon atoms such as methyl group, ethyl group and propyl group, the lower alkoxy groups include those having 1 to 5 carbon atoms such as methoxy group, ethoxy group and propoxy group, and the lower alkylamino groups are those having 1 to 5 carbon atoms such as monomethylamino group, monoethylamino group and monopropylamino group. The lower acylated derivatives of the amino group and lower alkylamino groups are those acylated with fatty acids having 1 to 3 carbon atoms, such as formylamino group, acetylamino group, propionylamino group, formylmethylamino group, formylethylamino group, formylpropylamino group, acetylmethylamino

group, acetylethylamino group, acetylpropylamino group, propionylmethylamino group, propionylethylamino group and propionylpropylamino group. The dialkylamino groups include, for example, lower alkylamino groups having 2 to 7 carbon atoms in total  
5 such as dimethylamino group, diethylamino group and methylethylamino group. The cycloalkylamino groups include amino groups having a 4- to 7-membered ring such as azetidino group, pyrrolidino group, piperidino group, homopiperidino group, piperazino group and morpholino group. The  $-O(CH_2)_nO-$  groups include methylenedioxy group, ethylenedioxy  
10 group and propylenedioxy group. In those atoms and groups, the halogen atoms are preferably fluorine atom and chloride atom, and the lower alkyl groups are preferably those having 1 to 3 carbon atoms. The lower alkoxy groups are preferably those having 1 to 3 carbon atoms. The monoalkylamino groups are preferably lower monoalkylamino groups  
15 having 1 to 3 carbon atoms. The dialkylamino groups are preferably those wherein the alkyl groups have 2 to 6 carbon atoms in total. The cycloalkylamino groups are preferably those wherein the ring has 4 to 6 members. The acyl groups in the lower acylated derivatives of the amino group and those lower alkylamino groups are preferably formyl group or  
20 acetyl group. It is preferred that  $R^9$  to  $R^{13}$  are not a hydrogen atom at the same time.

In the above general formula [I] and also in general formulae [XV] and [XVI], the following conditions are preferred:

- (i) X and Z are bonded together to form  $CH_2-CH_2$  or  $CH_2-CH_2-CH_2$  and Y  
25 represents a hydrogen atom,  
(ii) Y and Z are bonded together to form  $CH_2-CH_2-CH_2$  or  $CH_2-CH_2-CH_2-$

CH<sub>2</sub> and X represents a hydrogen atom,

(iii) X and Y are each a hydrogen atom and Z is a lower alkyl group,

(iv) either or both of R<sup>10</sup> and R<sup>11</sup> are methoxyl group or R<sup>10</sup> and R<sup>11</sup> together form methylenedioxy group, and R<sup>9</sup>, R<sup>12</sup> and R<sup>13</sup> are each a hydrogen atom,

(v) R<sup>11</sup> is methoxyl group, and R<sup>9</sup>, R<sup>10</sup>, R<sup>12</sup> and R<sup>13</sup> are each a hydrogen atom,

(vi) either R<sup>10</sup> or R<sup>11</sup> is amino group, a lower alkylamino group, a lower acylated amino group, a lower acylated lower alkylamino group, a lower dialkylamino group or a cycloalkylamino group, and the other is a hydrogen atom,

(vii) all of R<sup>1</sup> and R<sup>8</sup> are a hydrogen atom,

(viii) one of R<sup>1</sup> and R<sup>8</sup> is fluorine atom or chlorine atom and the others are each a hydrogen atom,

(ix) one of R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and R<sup>7</sup> is fluorine atom or chlorine atom and others are each a hydrogen atom,

(x) A and B-D are both CH<sub>2</sub>,

(xi) the carbon atom to which X is bonded has an absolute configuration of R,

(xii) the carbon atom to which X is bonded has an absolute configuration of S,

(xiii) the carbon atom to which Y is bonded has an absolute configuration of R, and

(xiv) the carbon atom to which Y is bonded has an absolute configuration of S,

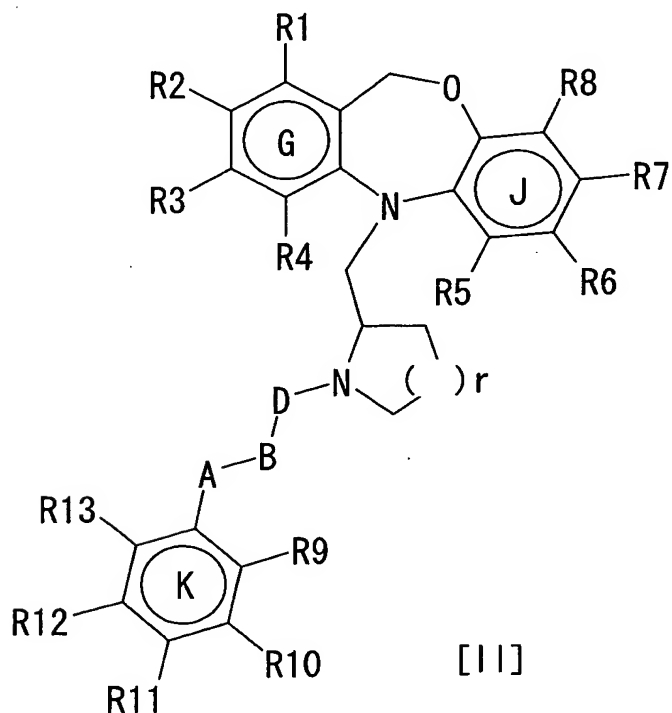
The cyclic amino groups represented by the formula [E] include



those having one nitrogen atom such as azetidino group, pyrrolidino group and piperidino group and also those further containing a hetero atom such as nitrogen atom or oxygen atom, such as piperazino group and morpholino group. In those groups, pyrrolidino group and morpholino group are preferred. It is more preferred that in  $R^9$  to  $R^{13}$ , either  $R^{10}$  or  $R^{11}$  is a cyclic amino group and the other is a hydrogen atom.

A-B-D is preferably  $\text{CH}_2\text{-CH}_2$ ,  $\text{CO-CH}_2$ ,  $\text{CHOH-CH}_2$ ,  $\text{CHOH-CH}_2\text{-CH}_2$ ,  $\text{CH}_2\text{-CHOH-CH}_2$ ,  $\text{CH=CH-CH}_2$ ,  $\text{CO-CH}_2\text{-CH}_2$ ,  $\text{O-CH}_2\text{-CH}_2$ ,  $\text{CH}_2\text{-CO-CH}_2$  or  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ .

In these compounds, preferred ones are those represented by the following formula [II] wherein G, J, K,  $R^1$  to  $R^{13}$ , A, B and D are the same as those in the above formula [I], and r represents 1 or 2:



The compounds of the formula [II] are, for example, 2-fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e]-

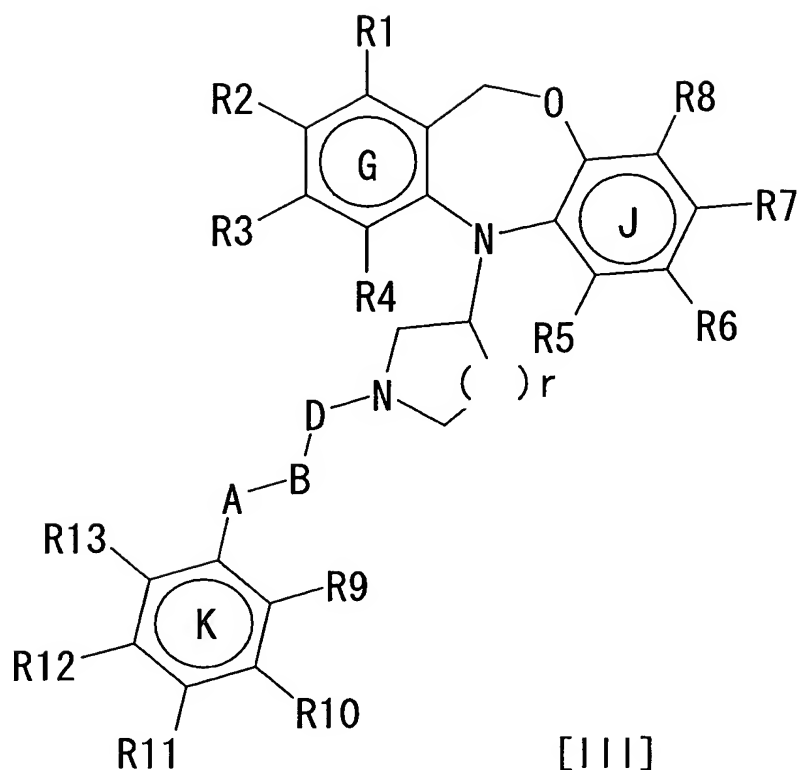
[1,4]-oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-methoxyphenethyl)-  
 pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-  
 5-[1-(3,4-methylenedioxyphenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e]-  
 [1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(4-aminophenethyl)pyrrolidin-  
 5 2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-  
 aminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 2-  
 fluoro-5,11-dihydro-5-[1-(4-methylaminophenethyl)pyrrolidin-2-yl-  
 methyl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-methyl-  
 aminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 2-  
 10 fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-yl-  
 methyl]dibenzo[b,e][1,4]-oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-  
 dimethylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]-  
 oxazepine, 2-fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-  
 2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-  
 15 pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine,  
 2-fluoro-5,11-dihydro-5-[1-(4-morpholinophenethyl)pyrrolidin-2-yl-  
 methyl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-  
 morpholinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine,  
 2-fluoro-5,11-dihydro-5-[1-(4-phlorophenethyl)pyrrolidin-2-ylmethyl]di-  
 20 benzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-phlorophenethyl)-  
 pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-  
 5-[1-(4-acetylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]-  
 oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-acetylaminophenethyl)-  
 pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-  
 25 5-[1-(4-methoxyphenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]-  
 oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-methoxyphenethyl)pyrrolidin-2-

ylmethyl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]-oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-aminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e]-[1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-aminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-methylaminophenethyl)pyrrolidin-2-yl-methyl]-dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-methylamino-phenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]-oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-ylmethyl]-dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-dimethylamino-phenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e]-[1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-morpholinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]-oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-morpholinophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]-oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-phlorophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-phlorophenethyl)pyrrolidin-2-ylmethyl]-dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-acetylamino-phenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-acetylamino-phenethyl)pyrrolidin-2-ylmethyl]-dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e]-[1,4]oxazepine, 5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-[1-(4-piperidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo-

[b,e][1,4]oxazepine, 5,11-dihydro-5-[1-(3-piperidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e]-[1,4]oxazepine, 5,11-dihydro-5-[1-(4-morpholino-phenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-[1-(3-morpholinophenethyl)pyrrolidin-2-ylmethyl]dibenzo-  
5 [b,e][1,4]oxazepine, and their isomers having a different position of the halogen substitution, pharmacologically acceptable salts, hydrates and solvates of them.

The compounds [II] of the present invention having one or more asymmetric carbon atoms can be optical isomers. Those optical isomers,  
10 mixtures of them and racemic compounds of them are included in the compounds of the present invention. In those compounds, the configuration in the 2-position of pyrrolidine ring or piperidine ring bonded to the dihydrodibenzoxazepine ring through methylene is preferably R.

15 Other preferred compounds are, for example, those of the following formula [III]:



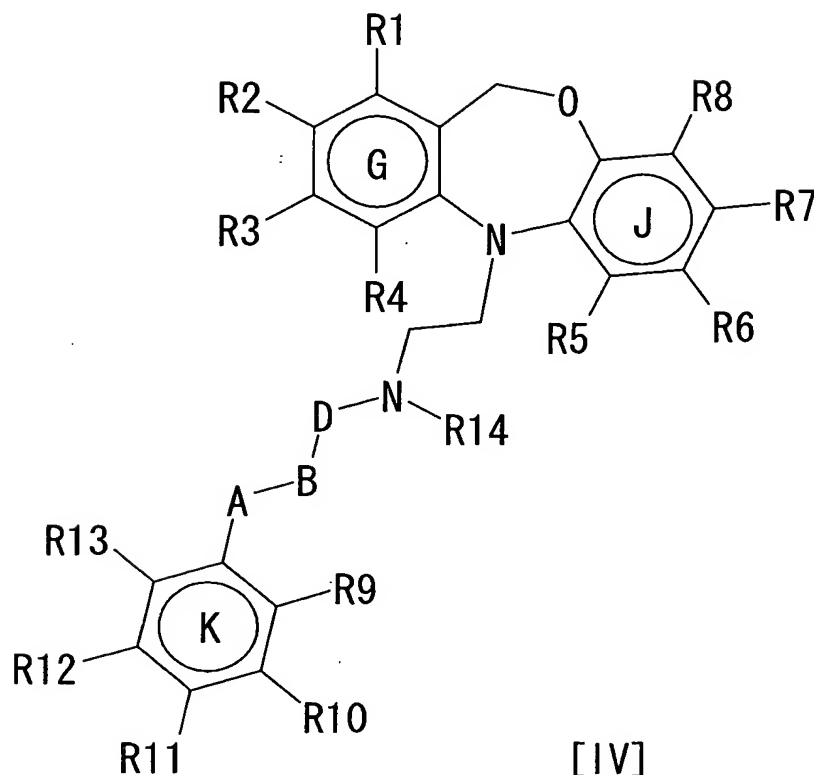
wherein aromatic rings G, J and K, R<sup>1</sup> to R<sup>13</sup>, A, B and D are the same as those in the above formula [I], and r represents 1 or 2. The compounds of the formula [III] are, for example, 2-fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)-pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-methoxyphenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)-pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(4-aminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-aminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-oxazepine, 2-fluoro-5,11-dihydro-5-[1-(4-methylaminophenethyl)-pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-methylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-3-yl]-

dibenzo[b,e][1,4]-oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-dimethyl-  
 aminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-  
 5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo[b,e]-  
 [1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)-  
 5 pyrrolidin-3-yl]di-benzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(4-  
 morpholinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-oxazepine, 2-  
 fluoro-5,11-dihydro-5-[1-(3-morpholinophenethyl)pyrrolidin-3-yl]dibenzo-  
 [b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(4-phlorophenethyl)-  
 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-  
 10 phlorophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 2-fluoro-  
 5,11-dihydro-5-[1-(4-acetylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e]-  
 [1,4]-oxazepine, 2-fluoro-5,11-dihydro-5-[1-(3-acetylaminophenethyl)-  
 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-  
 methoxyphenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-oxazepine, 3-chloro-  
 15 5,11-dihydro-5-[1-(3-methoxyphenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-  
 oxazepine, 3-chloro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)-  
 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-  
 aminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-  
 5,11-dihydro-5-[1-(3-aminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-  
 20 oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-methylaminophenethyl)-  
 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-  
 methylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-  
 chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-3-yl]-  
 dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-dimethylamino-  
 25 phenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-  
 dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-

oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)-  
 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-  
 morpholinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-  
 chloro-5,11-dihydro-5-[1-(3-morpholinophenethyl)pyrrolidin-3-yl]dibenzo-  
 5 [b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(4-fluorophenethyl)-  
 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-  
 fluorophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 3-chloro-  
 5,11-dihydro-5-[1-(4-acetylamino-phenethyl)pyrrolidin-3-yl]dibenzo[b,e]-  
 [1,4]oxazepine, 3-chloro-5,11-dihydro-5-[1-(3-acetylamino-phenethyl)-  
 10 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-[1-(4-  
 pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 5,11-  
 dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-  
 oxazepine, 5,11-dihydro-5-[1-(4-piperidinophenethyl)pyrrolidin-3-yl]-  
 dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-[1-(3-piperidinophenethyl)-  
 15 pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-[1-(4-  
 morpholinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine, 5,11-  
 dihydro-5-[1-(3-morpholinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]-  
 oxazepine, and their isomers having a different position of the halogen  
 substitution, pharmacologically acceptable salts, hydrates and solvates of  
 20 them.

The compounds [III] of the present invention having one or more  
 asymmetric carbon atoms can have optical isomers. Those optical  
 isomers, mixtures of them and racemic compounds of them are included in  
 the compounds of the present invention. In those compounds, the  
 25 configuration in the 2-position of pyrrolidine ring or piperidine ring  
 bonded to the dihydrodibenzoxazepine ring is preferably R.

Other preferred compounds are, for example, those of the following formula [IV]:



wherein aromatic rings G, J and K, R<sup>1</sup> to R<sup>13</sup>, A, B and D are the same as  
 5 those in the above formula [I], and R<sup>14</sup> represents a lower alkyl group  
 having 1 to 3 carbon atoms.

The compounds of the formula [IV] are, for example, 2-fluoro-5,11-  
 dihydro-5-{2-[N-(4-methoxyphenethyl)-N-methyl]aminoethyl}dibenzo-  
 [b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(3-methoxyphenethyl)-  
 10 N-methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-  
 5-{2-[N-(3,4-methylenedioxyphenethyl)-N-methyl]aminoethyl}dibenzo-  
 [b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(4-aminophenethyl)-N-  
 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-



{2-[N-(3-aminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(4-methylaminophenethyl)-N-  
 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-  
 {2-[N-(3-methylaminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 5 oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(4-dimethylaminophenethyl)-N-  
 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-  
 {2-[N-(3-dimethylaminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e]-  
 [1,4]oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(4-pyrrolidinophenethyl)-N-  
 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-  
 10 {2-[N-(3-pyrrolidinophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(4-morpholino-phenethyl)-N-  
 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-  
 {2-[N-(3-morpholinophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(4-phlorophenethyl)-N-methyl]-  
 15 aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(3-  
 phlorophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 2-  
 fluoro-5,11-dihydro-5-{2-[N-(4-acetylaminophenethyl)-N-methyl]amino-  
 ethyl}dibenzo[b,e][1,4]oxazepine, 2-fluoro-5,11-dihydro-5-{2-[N-(3-acetyl-  
 aminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-  
 20 chloro-5,11-dihydro-5-{2-[N-(4-methoxyphenethyl)-N-methyl]amino-  
 ethyl}-dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(3-  
 methoxyphenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-  
 chloro-5,11-dihydro-5-{2-[N-(3,4-methylenedioxyphenethyl)-N-methyl]-  
 aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(4-  
 25 aminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-  
 chloro-5,11-dihydro-5-{2-[N-(3-aminophenethyl)-N-methyl]aminoethyl}-

dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(4-methyl-  
 aminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-  
 chloro-5,11-dihydro-5-{2-[N-(3-methylaminophenethyl)-N-methyl]amino-  
 ethyl}dibenzo[b,e][1,4]-oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(4-  
 5 dimethylaminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(3-dimethylaminophenethyl)-N-  
 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-  
 {2-[N-(4-pyrrolidinophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(3-pyrrolidinophenethyl)-N-  
 10 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-  
 {2-[N-(4-morpholinophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(3-morpholinophenethyl)-N-  
 methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-  
 {2-[N-(4-phlorophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]-  
 15 oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(3-phlorophenethyl)-N-methyl]-  
 aminoethyl}dibenzo[b,e][1,4]oxazepine, 3-chloro-5,11-dihydro-5-{2-[N-(4-  
 acetylaminophenethyl)-N-methyl]aminoethyl}dibenzo[b,e][1,4]oxazepine,  
 3-chloro-5,11-dihydro-5-{2-[N-(3-acetylaminophenethyl)-N-methyl]amino-  
 ethyl}dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-{2-[N-methyl-N-(4-  
 20 pyrrolidinophenethyl)]aminoethyl}dibenzo[b,e][1,4]oxazepine, 5,11-  
 dihydro-5-{2-[N-methyl-N-(3-pyrrolidinophenethyl)]aminoethyl}dibenzo-  
 [b,e][1,4]oxazepine, 5,11-dihydro-5-{2-[N-methyl-N-(4-pipelidino-  
 phenethyl)]aminoethyl}dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-{2-[N-  
 methyl-N-(3-piperidinophenethyl)]aminoethyl}dibenzo[b,e][1,4]oxazepine,  
 25 5,11-dihydro-5-{2-[N-methyl-N-(4-morpholinophenethyl)]aminoethyl}-  
 dibenzo[b,e][1,4]oxazepine, 5,11-dihydro-5-{2-[N-methyl-N-(3-

morpholinophenethyl)]aminoethyl}dibenzo[b,e][1,4]-oxazepine, and their isomers having a different position of the halogen substitution, pharmacologically acceptable salts, hydrates and solvates of them.

In the present invention, preferred derivatives are (i) derivatives  
5 of the formula [I] wherein one of  $R^9$  to  $R^{13}$  is a cyclic amino group of formula [E] and the others are each a hydrogen atom and  $R^1$  to  $R^8$  are each a hydrogen atom, (ii) derivatives of the formula [I] wherein one of  $R^9$  to  $R^{13}$  is a cyclic amino group of formula [E] and the others are each a hydrogen atom and one or two of  $R^1$  to  $R^8$  are a hydrogen atom or chlorine atom and  
10 (iii) derivatives of the formula [I] wherein all of  $R^9$  to  $R^{13}$  are a group other than the cyclic amino group of formula [E] and one or two of  $R^1$  to  $R^8$  are a hydrogen atom or chlorine atom and the others are each a hydrogen atom.

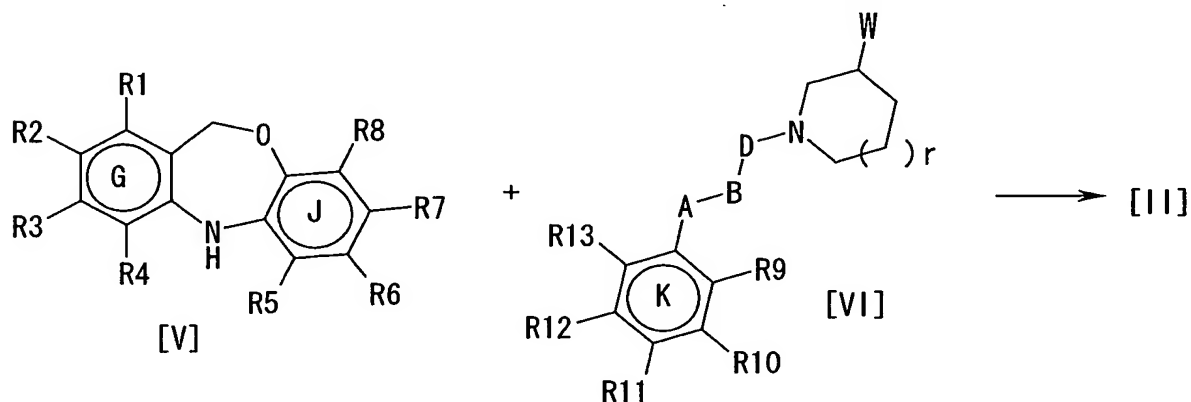
In general formulae [XV] and [XVI], preferably (i)  $R^1$  to  $R^8$  may be the same or different from each other and they each represent fluorine  
15 atom, chlorine atom or a hydrogen atom,  $L_1$ -  $L_2$  represents  $CH_2$  or  $CH_2$ - $CH_2$ , Y and Z are bonded together to form  $CH_2$ - $CH_2$ - $CH_2$  or  $CH_2$ - $CH_2$ - $CH_2$ - $CH_2$ , and/or (ii)  $R^9$  to  $R^{13}$  may be the same or different from each other and they each represent a hydrogen atom, amino group, a lower alkylamino group, lower acylated amino group, a lower acylated alkylamino group, a  
20 lower dialkylamino group or a cycloalkylamino group.

Concretely, preferred compounds are (R)-{[2-(3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine-5-carbonyl)pyrrolidine]-1-yl}-2-(4-dimethylaminophenyl)ethanone, (R)-1-[(4-dimethylaminophenyl)acetyl]-pyrrolidine-2-carboxylic acid [2-(2-bromo-4-chlorobenzyloxy)phenyl]-  
25 amide, (R)-{[2-(2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine-5-carbonyl)pyrrolidine]-1-yl}-2-(4-pyrrolidinophenyl)ethanone, (R)-1-[(4-

pyrrolidinophenyl)acetyl]pyrrolidine-2-carboxylic acid [2-(2-bromo-5-fluorobenzyloxy)phenyl]amide, and stereoisomers and salts thereof.

The pharmacologically acceptable salts of the compounds [I] of the present invention are, for example, mineral acid salts (inorganic salts) such as hydrochlorides, hydrobromides, sulfates and phosphates, and organic acid salts such as acetates, lactates, fumarates, maleates, malates, tartrates, citrates, oxalates, aspartates and methanesulfonates.

In the compounds [I] of the present invention, those represented by the formula [III] can be produced by, for example, the following process (reaction formula 1) disclosed in International Patent No. 9733885A1:



reaction formula 1

wherein aromatic rings G, J and K,  $R^1$  to  $R^{13}$ , A, B and D are the same as those in the above formula [I], r represents 1 or 2, and W represents a halogen atom such as chlorine atom, bromine atom or iodine atom.

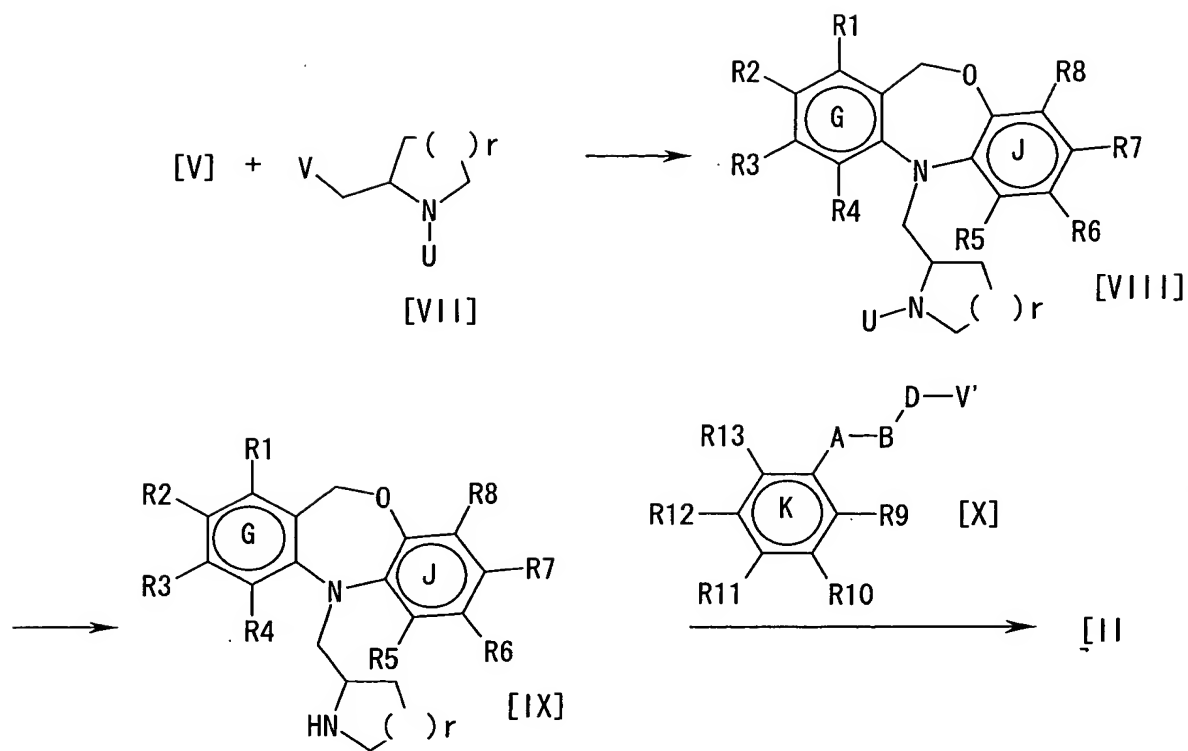
The compounds [II] of the present invention can be produced by reacting a compound [V] with a compound of the above general formula [VI] in the presence of a base in a solvent. The preferred solvents for the

reaction are, for example, dimethyl sulfoxide, amides such as N,N-dimethylformamide, ethers such as tetrahydrofuran, diethyl ether, dioxane and 1,2-dimethoxyethane, acetonitrile, toluene, xylene and benzene. The bases are, for example, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, lithium diisopropylamide, n-butyllithium, sodium methoxide and potassium t-butoxide. The reaction temperature is in the range of usually 0 to 150°C, preferably room temperature to 100°C. The reaction time which varies depending on the reaction temperature or variety of the solvent is usually 1 to 50 hours. The amount of the compound [VI] and the base is 0.5 to 5 molar equivalents, preferably 0.8 to 2 molar equivalents, per molar equivalent of the compound [V], respectively.

The compounds [V] used as the starting material in the above-described reaction can be produced by a well-known process [J. Med. Chem., 7, 609 (1964)].

The halides represented by the above general formula [VI] can be produced by a method disclosed in European Patent No. 0404359A1, which comprises the steps of reducing proline or homoproline used as the starting material to obtain an alcohol, N-alkylating the alcohol and then halogenating the hydroxyl group of the compound with ring expansion using methanesulfonyl chloride, tosyl chloride or the like.

The compounds [II] of the present invention can be produced by, for example, the following process (reaction formula 2) disclosed in International Patent No. 9912925A1:



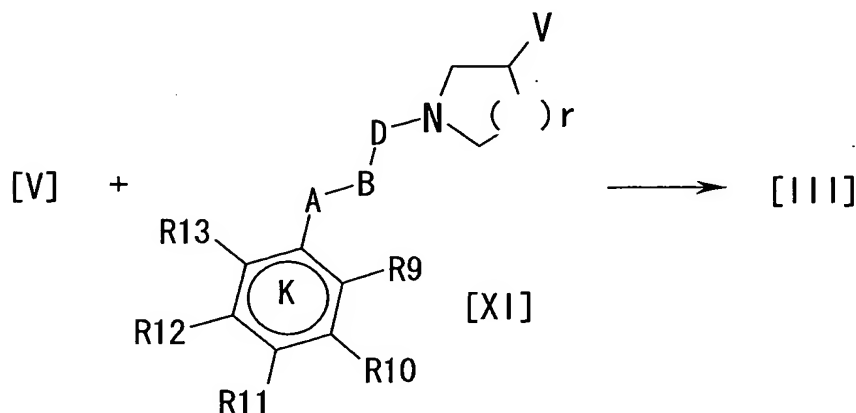
reaction formula 2

wherein aromatic rings G, J and K,  $R^1$  to  $R^{13}$ , A, B and D are the same as those in the above formula [I], r represents 1 or 2, V and V' each represent  
 5 chlorine atom, bromine atom, iodine atom or a leaving group such as tosyloxyl group or mesyloxyl group and U represents a protecting group for the amino group such as t-butyloxycarbonyl group, benzyloxycarbonyl group and tosyl group.

The compounds [II] of the present invention can be produced by  
 10 adding, for example, N-t-butyloxycarbonyl-2-piperidylmethyl tosylate of the above general formula [VII] dropwise to a compound [V] in the presence of a base to carry out the invention, removing the protecting group from the obtained compound of the general formula [VIII] to obtain a compound of the general formula [IX], and then reacting this compound

with a compound of the general formula [X] in the presence of a base. The solvents and bases used for the reactions for obtaining [VIII] from [V] and also for obtaining [II] from [IX] can be those used for the reaction of the above formula 1.

5 In the compounds [I] of the present invention, those represented by the formula [III] can be produced by, for example, the following process (reaction formula 3) disclosed in International Patent No. 0040570A1:



reaction formula 3

wherein aromatic ring K, R<sup>9</sup> to R<sup>13</sup>, A, B, D, V and r are the same as those in the above reaction formula 2.

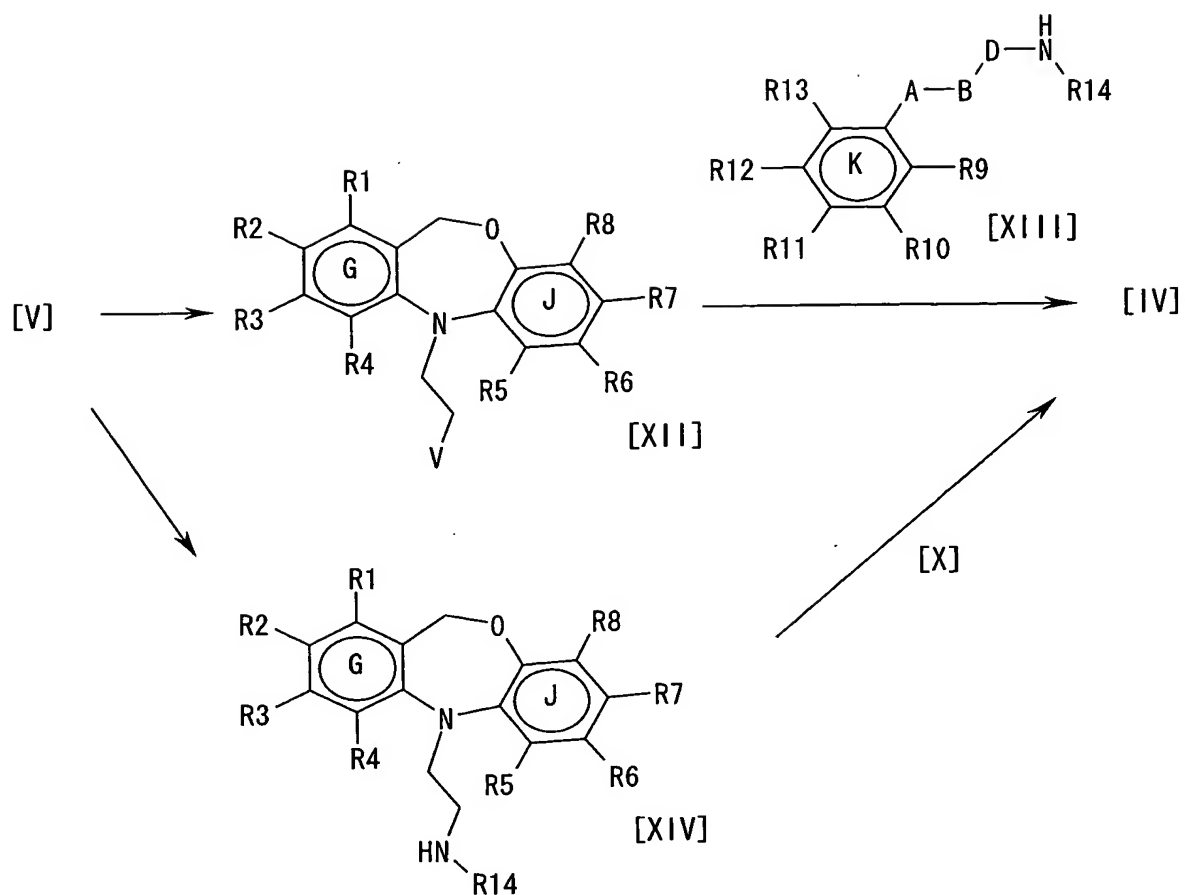
10 The compounds [III] of the present invention can be produced by reacting a compound [V] with a compound of the above general formula [XI] in the presence of a base in a solvent. The preferred solvents for the reaction are, for example, dimethyl sulfoxide, amides such as N,N-dimethylformamide, ethers such as tetrahydrofuran, diethyl ether,  
 15 dioxane and 1,2-dimethoxyethane, acetonitrile, toluene, xylene and benzene. The bases are, for example, sodium hydride, potassium hydride, lithium diisopropylamide, n-butyllithium, sodium methoxide and potassium t-butoxide. The reaction temperature is in the range of

usually 0 to 150°C, preferably room temperature to 100°C. The reaction time which varies depending on the reaction temperature or variety of the solvent is usually 1 to 50 hours. The amount of the compound [XI] and the base is 0.5 to 10 molar equivalents, preferably 0.8 to 5 molar equivalents, per molar equivalent of the compound [V], respectively.

The compounds of the general formula [XI] can be obtained by N-alkylating 3-hydroxypyrrolidine or 3-hydroxypiperidine and then reacting the obtained product with phosphorus oxychloride, thionyl chloride, tosyl chloride, methanesulfonyl chloride or the like.

10 In the compounds [I] of the present invention, those represented by the formula [IV] can be produced by, for example, the following process (reaction formula 4) disclosed in International Patent No. 0040570A1:





reaction formula 4

wherein aromatic rings G, J and K, R<sup>1</sup> to R<sup>13</sup>, A, B, D and V are the same as those described above and R<sup>14</sup> represents a lower alkyl group.

Namely, the compounds [IV] of the present invention can be produced by converting a compound [V] into a compound of the above general formula [XII] and then this compound is reacted with a compound of the above general formula [XIII] in the presence of a base. The preferred solvents for the reaction are, for example, dimethyl sulfoxide, amides such as N,N-dimethylformamide, ethers such as tetrahydrofuran, diethyl ether, dioxane and 1,2-dimethoxyethane, acetonitrile, toluene, xylene and benzene. The bases are, for example, sodium carbonate,

potassium carbonate, sodium hydride, potassium hydride, lithium diisopropylamide, n-butyllithium, sodium methoxide and potassium t-butoxide. The reaction temperature is in the range of usually 0 to 150°C, preferably room temperature to 100°C. The reaction time which varies  
5 depending on the reaction temperature or variety of the solvent is usually 1 to 50 hours. The amount of the base is at least 1 mole, preferably 1 to 5 moles per mole of the compound [XII]. The amount of the compound [XII] is 0.5 to 2 moles, preferably 0.7 to 1.5 moles, per mole of the compound [XIII].

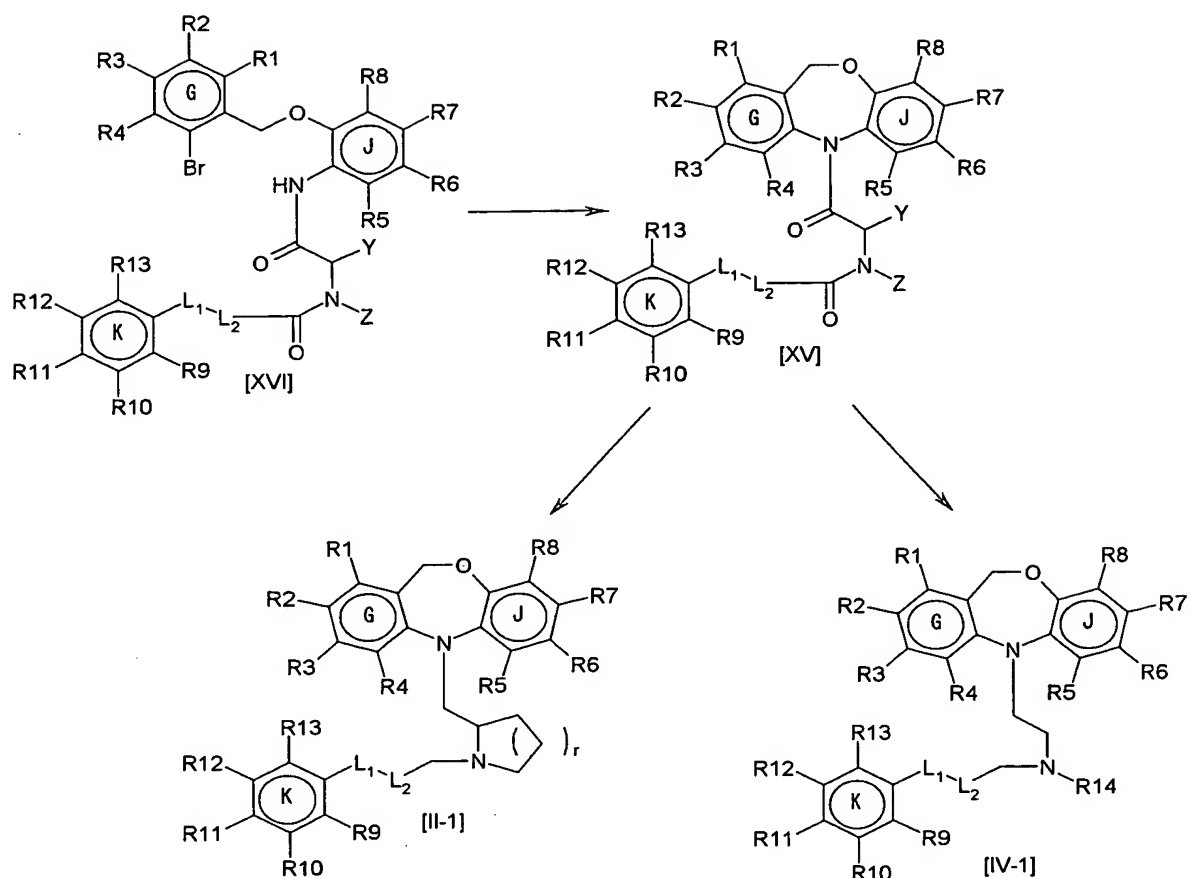
10 The compounds [IV] of the present invention can be produced by converting a compound [V] into a compound of the above general formula [XIV] and then condensing the obtained compound with a compound [X] in the presence of a base. In the condensation reaction, the solvent, base, reaction temperature and reaction time may be the same as those  
15 described above. The amount of the base used is at least 1 mole, preferably 1 to 5 moles per mole of the compound [XIV]. The amount of the compound [XIV] is 0.5 to 2 moles, preferably 0.7 to 1.5 moles, per mole of the compound [X].

The compounds [XII] can be easily produced by combining known  
20 methods. For example, the compounds [XII] can be produced by alkylating the compound [V] with an  $\alpha$ -haloacetic acid ester, reducing the obtained compound to form an alcohol and then converting the hydroxyl group thereof into a leaving group, or by alkylating the compound [V] with a 2-haloethanol wherein the hydroxyl group is protected, removing  
25 the protecting group and converting the hydroxyl group into a leaving group. The compounds [XIII] can be easily produced by various known

processes such as the alkylation reaction of the primary amine with a corresponding halide, the reduction alkylation reaction of a primary amine with a corresponding aldehyde or the acylation of an amine with a corresponding carboxylic acid followed by the reduction as disclosed in  
5 International Patent No. 0040570A1.

Compounds [XIV] can be easily produced by various known processes such as the alkylation of the compound [V] with a haloacetic acid ester followed by the amidation and reduction as disclosed in International Patent No. 0040570A1.

10 In addition to the above-described processes, compounds represented by the formula [II] or [IV] in the compounds [I] of the present invention can be produced via compounds represented by formulae [XVI] and [XV] given below by methods similar to those disclosed in International Patent No. 0117980A1. Namely, when a compound of the  
15 formula [II] is represented by the formula [II-1] and a compound of the formula [IV] is represented by the formula [IV-1], each of them can be obtained through a corresponding intermediate by the intramolecular arylation of a compound of the following formula [XVI] to form a compound of the formula [XV], followed by the reduction of the obtained  
20 compound according to the following reaction formula 5.



reaction formula 5

wherein aromatic rings G, J and K, R<sup>1</sup> to R<sup>14</sup>, L<sub>1</sub> and L<sub>2</sub> are as defined in the formula [XV], r represents 1 or 2, Y and Z are bonded together to form CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub> or CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>, or when Y and Z are not bonded together, Y represents a hydrogen atom and Z represents a lower alkyl group.

The solvents used in the reduction reaction include ethers such as diethyl ether, dioxane, tetrahydrofuran and 1,2-dimethoxyethane. The solvents may contain 0 to 50 % of benzene, toluene, xylene, etc. The reducing agents are, for example, borane compounds such as diborane, borane / ammonia complex, borane / tert-butylamine complex, borane /

N,N-diethylaniline complex, borane / N,N-diisopropylethylamine complex, borane / dimethylamine complex, borane / 4-(dimethylamino)pyridine complex, borane diphenylphosphine complex, borane / 4-ethylmorpholine complex, borane / 2,6-lutidine complex, borane / 4-methylmorpholine complex, borane / dimethyl sulfide complex, borane / morpholine complex, borane / 1,4-oxathiane complex, borane / 4-phenylmorpholine complex, borane / pyridine complex, borane / tetrahydrofuran complex, borane tributylphosphine complex, borane / triethylamine complex, borane / trimethylamine complex and borane / triphenylphosphine complex; metal hydrides such as aluminum lithium hydride, sodium borohydride and lithium borohydride; as well as those compounds further substituted with an alkyl, alkoxyl or acyl group. A reducing agent may be prepared by adding an acid or the like to the above-described metal halide in the reaction vessel. The acids usable herein include, for example, Brønsted acids such as hydrochloric acid, sulfuric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphor sulfonic acid, acetic acid and trifluoroacetic acid; Lewis acids such as boron trifluoride, boron trichloride and aluminum trichloride as well as complexes thereof. A process wherein, for example, diborane or borane tetrahydrofuran complex is selectively used in the above-described reducing agents, or a process wherein methanesulfonic acid, boron trifluoride, a complex thereof or the like is added to sodium borohydride to prepare the reducing agent in the reactor is preferred. The reaction temperature that varies depending on the boiling point of the solvent is usually in the range of usually 5 to 100°C, preferably 30 to 60°C. The reaction time that varies depending on the variety of the reducing agent, reaction temperature or

variety of the solvent is usually 4 to 70 hours. The amount of the reducing agent, which varies depending on the variety thereof, is such that the amount of the hydride that can be formed will be at least 4 moles, preferably at least 7 moles per mole of the same. The compounds [II-1] to compounds [IV-1] obtained by the reaction can be purified by the silica gel column chromatography, crystallization or the like. Further, the compounds [II-1] to compounds [IV-1] can be crystallized in the form of a salt thereof with a suitable acid. The salts of these compounds with a suitable acid are mineral acid salts (inorganic salts) of them such as hydrochlorides, hydrobromides, sulfates and phosphates, and organic acid salts of them such as acetates, lactates, fumarates, maleates, malates, tartrates, citrates, oxalates, aspartates and methanesulfonates.

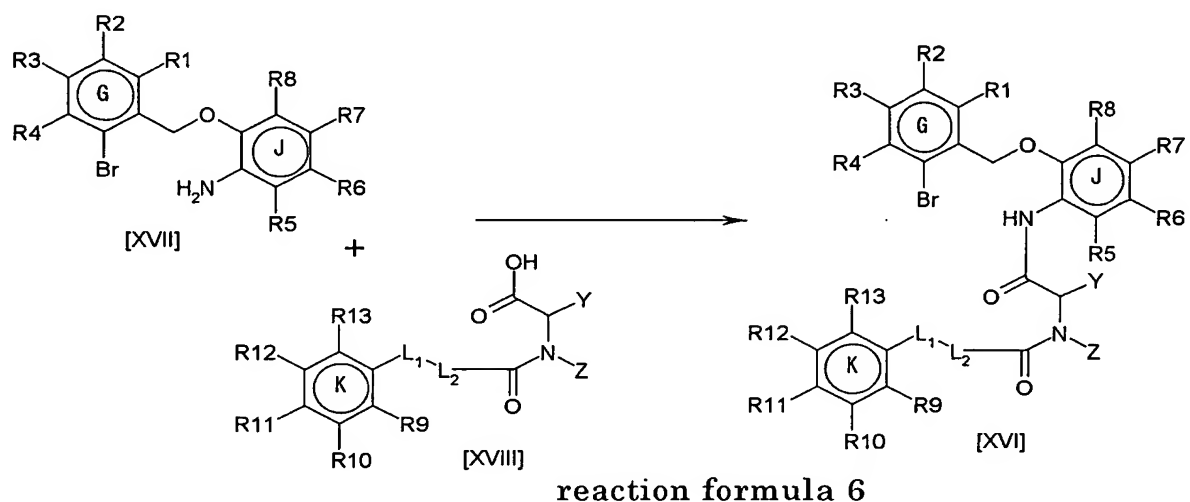
The compounds [XV] used as the starting materials in the reduction reaction can be produced by the intramolecular arylation of the compounds [XVI] in the presence of a base and a metallic catalyst. The solvents for the reaction are, for example, unsubstituted and substituted benzene, unsubstituted and substituted pyridine, and amides such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidone. In those reaction solvents, for example, toluene, pyridine, picoline and N-methylpyrrolidone are preferably usable. The bases are, for example, carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, calcium carbonate and cesium carbonate; metal alkoxides such as sodium methoxide, sodium t-butoxide and potassium t-butoxide; and amines such as trimethylamine, triethylamine, diisopropylethylamine and N-methylmorpholine. In those bases, for example, sodium carbonate, potassium carbonate and

cesium carbonate are preferably used. The metallic catalysts include copper catalysts such as copper, copper (I) chloride, copper (I) bromide and copper (I) iodide; palladium catalysts such as palladium, palladium chloride, palladium acetate and tetrakis(triphenylphosphine) palladium, and complexes of them; platinum catalysts such as platinum and platinum chloride and complexes of them. In those metal catalysts, for example, copper and copper (I) bromide are preferably used. The metal catalysts may also be prepared in the reactor. The reaction temperature that varies depending on the boiling point of the solvent is usually in the range of room temperature to 200°C, preferably 100 to 150°C. The reaction time that varies depending on the varieties of the base and metallic catalyst, reaction temperature or variety of the solvent is usually 8 to 200 hours. The amount of the base, that varies depending on the variety thereof, is usually 1 to 10 moles, preferably 1 to 4 moles, per mole of the compound. The amount of the metallic catalyst, that varies depending on the variety thereof, is usually 0.001 to 1 mole, preferably 0.005 to 0.2 mole, per mole of the compound. The compounds [XV] obtained by the reaction can be purified by the extraction from the reaction mixture, the silica gel column chromatography, crystallization or the like before the subsequent reaction or, on the contrary, they can be subjected to the subsequent reaction as they are. Further, the compounds [XV] can be obtained in the form of a salt thereof with a suitable acid. The salts of these compounds with a suitable acid are mineral acid salts (inorganic salts) of them such as hydrochlorides, hydrobromides, sulfates, phosphates and nitrates, and organic acid salts of them such as acetates, lactates, fumarates, maleates, malates,

tartrates, citrates, oxalates, aspartates and methanesulfonates.

The compounds [XVI] used as the starting materials for the above-described intramolecular arylation reaction can be produced by the following process (reaction formula 6):

5



wherein aromatic rings G, J and K,  $R^1$  to  $R^{13}$ ,  $L_1$  and  $L_2$  are as defined in the formula [XVI], Y and Z are bonded together to form  $CH_2-CH_2-CH_2$  or  $CH_2-CH_2-CH_2-CH_2$ , or when Y and Z are not bonded together, Y represents a hydrogen atom and Z represents a lower alkyl group.

10

Namely, compounds [XVI] can be produced by condensing a compound [XVII] with a compound [XVIII]. The condensation reaction process can be selected from known processes such as an amidation reaction wherein N,N'-dicyclohexylcarbodiimide or N-dimethylaminopropyl-N'-ethylcarbodiimide or a salt thereof is used, an acid anhydride process wherein a compound [XVIII] is converted into a corresponding acid anhydride prior to the condensation, and a process wherein the product is obtained *via* a corresponding acid chloride or acid bromide of the compound [XVIII]. The compound [XVI] obtained by the

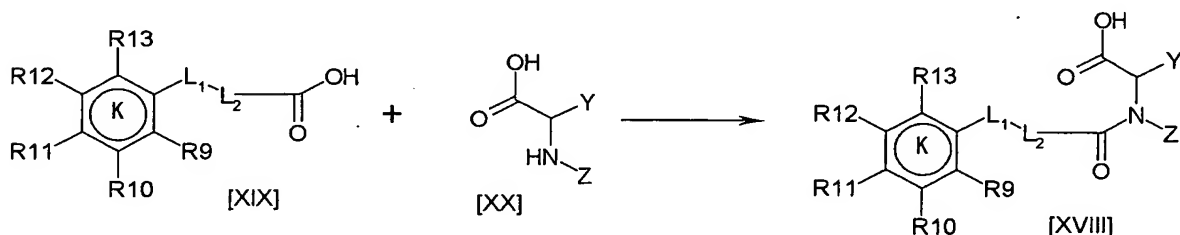
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reaction can be extracted from the reaction mixture and purified by the silica gel column chromatography, crystallization or the like before the subsequent reaction or, on the contrary, it can be directly subjected to the subsequent reaction. Further, the compounds [XVI] can be obtained in the form of a salt thereof with a suitable acid. The salts of these compounds with a suitable acid are mineral acid salts (inorganic salts) of them such as hydrochlorides, hydrobromides, sulfates, phosphates and nitrates, and organic acid salts of them such as acetates, lactates, fumarates, maleates, malates, tartrates, citrates, oxalates, aspartates and methanesulfonates.

The compounds [XVII] used as the starting materials for the above-described reaction 6 can be produced by a known method [J. Med. Chem., 7, 609 (1964)].

The compounds [XVIII] can be produced by the following process (reaction formula 7):



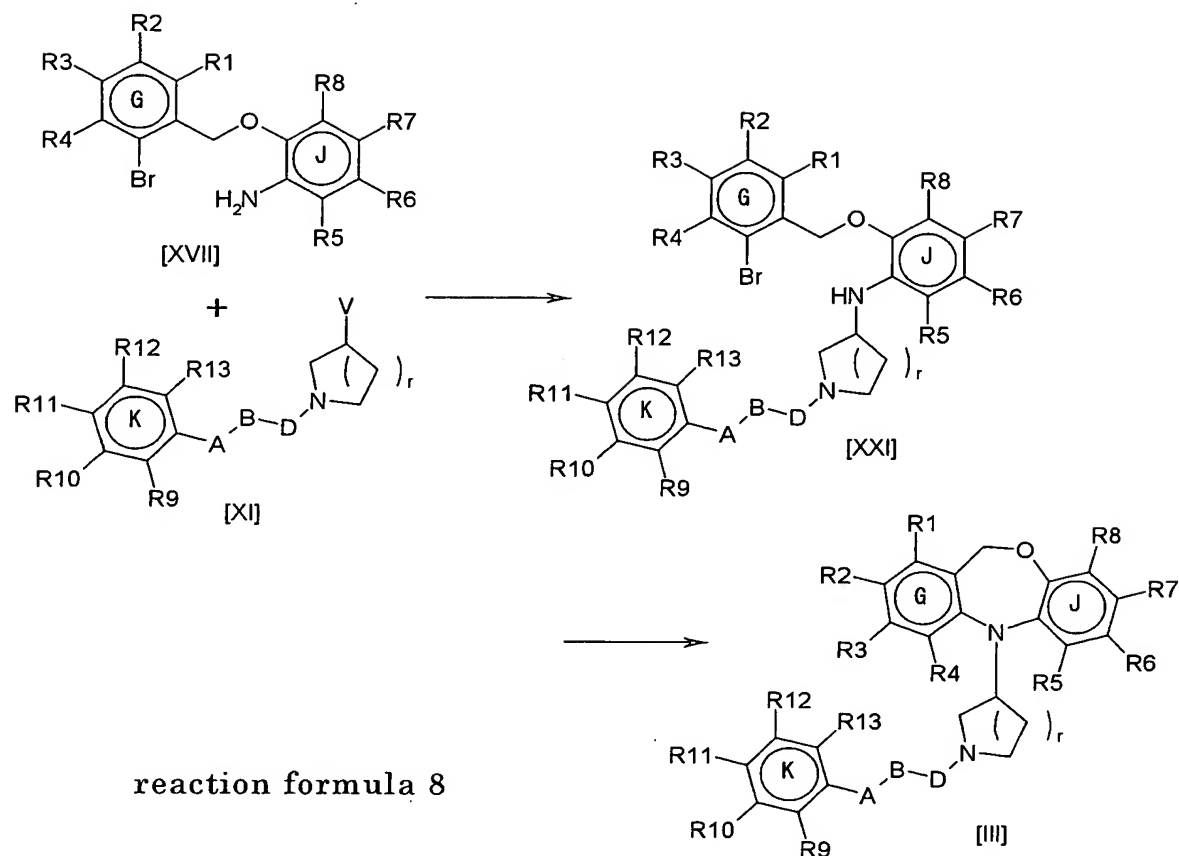
reaction formula 7

wherein aromatic ring K, R<sup>9</sup> to R<sup>13</sup>, L<sub>1</sub> and L<sub>2</sub> are as defined above, Y and Z are bonded together to form CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub> or CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>, or when Y and Z are not bonded together, Y represents a hydrogen atom and Z represents a lower alkyl group.

Namely, compounds [XVIII] can be produced by condensing a compound [XIX] with a compound [XX]. The condensation reaction can

be selected from known processes such as an amidation reaction wherein N,N'-dicyclohexylcarbodiimide or N-dimethylaminopropyl-N'-ethylcarbodiimide or a salt thereof is used, an acid anhydride process wherein a compound [XIX] is converted into a corresponding acid anhydride prior to the condensation, and a process wherein the product is obtained *via* a corresponding acid chloride or acid bromide of the compound [XIX]. The compound [XVIII] obtained by the reaction can be extracted from the reaction mixture and purified by the silica gel column chromatography, crystallization or the like before the subsequent reaction or, on the contrary, it can be directly subjected to the subsequent reaction. Further, the compounds [XVIII] can be produced by protecting the carboxylic acid part of the compound [XX] with a suitable protecting group and then removing the protecting group after the above-described condensation reaction with the compound [XIX]. The suitable protecting groups used herein are esters with methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl and substituted groups thereof, and silyl esters with trimethylsilyl, triethylsilyl and tert-butyldimethylsilyl groups.

In the compounds [I] of the present invention, those represented by the formula [III] can be produced by the following process (reaction formula 8):



wherein aromatic rings G, J and K, R<sup>1</sup> to R<sup>13</sup>, A, B, D, V and r are as defined above.

The compounds [III] can be produced by the intramolecular arylation of the compounds [XXI] in the presence of a base and a metallic catalyst. The solvents for the reaction are, for example, unsubstituted and substituted benzene, unsubstituted and substituted pyridine, and amides such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidone. The bases are, for example, carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, calcium carbonate and cesium carbonate; metal alkoxides such as sodium methoxide, sodium t-butoxide and potassium t-butoxide; and amines such

as trimethylamine, triethylamine, diisopropylethylamine and N-methylmorpholine. The metallic catalysts include copper catalysts such as copper, copper (I) chloride, copper (I) bromide and copper (I) iodide; palladium catalysts such as palladium, palladium chloride, palladium acetate and tetrakis(triphenylphosphine) palladium, and complexes of them; platinum catalysts such as platinum and platinum chloride and complexes of them. The metal catalysts may also be prepared in the reactor. The reaction temperature that varies depending on the boiling point of the solvent is usually in the range of room temperature to 200°C, preferably 80 to 160°C. The reaction time that varies depending on the varieties of the base and metallic catalyst, reaction temperature or variety of the solvent is usually 5 to 150 hours. The amount of the base, that varies depending on the variety thereof, is usually 1 to 20 moles, preferably 1.5 to 8 moles, per mole of the compound. The amount of the metallic catalyst, that varies depending on the variety thereof, is usually 0.001 to 1 mole, preferably 0.005 to 0.3 mole, per mole of the compound. The compounds [III] obtained by the reaction can be purified by the extraction from the reaction mixture, the silica gel column chromatography, high performance liquid chromatography, crystallization or the like. Further, the compounds [III] can be crystallized in the form of a salt thereof with a suitable acid. The salts of these compounds with a suitable acid are mineral acid salts (inorganic salts) of them such as hydrochlorides, hydrobromides, sulfates, phosphates and nitrates, and organic acid salts of them such as acetates, lactates, fumarates, maleates, malates, tartrates, citrates, oxalates, aspartates and methanesulfonates.

The compounds [XXI] used as the starting material for the

intramolecular arylation reaction can be produced by alkylating the amino group of compound [XVII] with compound [XI]. The alkylation reaction is carried out, for example, in the presence of a base. Namely, the compounds [XXI] can be produced by reacting compound [XVII] with  
5 compound [XI] in the presence of a base in a suitable solvent. The bases are, for example, carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, calcium carbonate and cesium carbonate, metal alkoxides such as sodium methoxide, sodium t-butoxide and potassium t-butoxide, and amines such as trimethylamine, triethylamine,  
10 diisopropylethylamine and N-methylmorpholine. The compounds [XXI] obtained by the reaction can be extracted from the reaction mixture and purified by the silica gel column chromatography or the like before the subsequent reaction or, on the contrary, it can be directly subjected to the subsequent reaction.

15 When the compounds of the present invention are used in the form of a pharmaceutical preparation or a pharmaceutical composition, they can be suitably mixed with pharmaceutical assistants such as pharmacologically acceptable excipient, carrier and diluent and orally or parenterally administered in the dosage form of tablets, capsules,  
20 granules, fine granules, powders, pills, syrups, suspensions, emulsions, ointments, suppositories or parenteral solution. In the present invention, a pharmaceutical preparation or a pharmaceutical composition containing one of the compounds of the present invention as the active ingredient, a pharmacologically acceptable carrier and/or diluent is  
25 preferred. The carriers and diluents are, for example, glucose, sucrose, lactose, talc, silica, cellulose, methylcellulose, starch, gelatin, ethylene

glycol, polyethylene glycol, glycerol, ethanol, water, oils and fats.

The dose and dosing frequency of the compounds of the present invention can be suitably selected depending on the kind of the disease, age and body weight of the patient, etc. For example, when a compound  
5 of the present invention is to be orally administered to an adult patient as a therapeutic agent for intestinal diseases such as irritable bowel syndrome, about 0.1 to 1,000 mg/day of the compound is given once or in several portions.

<Examples>

10 The following Examples, Test Examples and Preparation Examples will further illustrate the present invention, which by no means limit the invention.

[Example 1]

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-yl-  
15 methyl]dibenzo[b,e][1,4]oxazepine hydrochloride:

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine:

60 % sodium hydride (44 mg, 1.1 mmol) was washed with hexane in argon stream and then suspended in dimethyl sulfoxide (5 ml), and the obtained suspension was stirred at room temperature for 30 minutes. 3-Fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine (0.22 g, 1.0 mmol) was added to the suspension, and they were stirred at room temperature for 30 minutes and then at 50°C for additional 30 minutes. A solution of (R)-3-chloro-1-(4-methoxyphenethyl)piperidine (0.25 g, 1.0 mmol, prepared by a method disclosed in International Patent No. 9733885A1) in dimethyl sulfoxide (2 ml) was added dropwise to the obtained solution, and they were stirred at 50°C for 6 hours. The reaction mixture was distributed into saturated aqueous sodium chloride solution and ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (7:3) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-3-fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)piperidine-2-ylmethyl]dibenzo[b,e][1,4]-oxazepine in the form of a light yellow oily substance (0.30 g, 70 %).

E S I / M a s s : 4 3 3 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.60-1.90 (4H, m), 2.27 (1H, m), 2.50-2.60 (1H, m), 2.70-2.82 (3H, m), 2.98-3.10 (1H, m), 3.18-3.24 (1H, m), 3.35 (1H, dd, J=9.3, 12.9Hz), 3.82 (3H, s), 4.02 (1H, dd, J=3.60, 13.2Hz), 5.20 (1H, d, J=12.0Hz), 5.27 (1H, d, J=12.0Hz), 6.70-6.95 (6H, m), 6.98-7.05 (1H, m), 7.15-7.30 (4H, m)

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)piperidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine hydrochloride:

0.3 ml of 4 M hydrogen chloride / dioxane was added to a solution of (R)-3-fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)piperidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine (300 mg, 0.7 mmol) in dichloromethane (5 ml), and they were stirred together for 30 minutes. The solvent was  
5 evaporated under reduced pressure. The obtained residue was solidified with a mixed solvent of hexane and ethyl acetate. The solid thus precipitated was taken by the filtration to obtain the title compound in the form of a brown solid (257 mg, 79 %).

E S I / M a s s : 4 3 3 [M + H<sup>+</sup>]

10 NMR (CDCl<sub>3</sub>)  $\delta$  : 1.90–2.06 (1H, m), 2.06–2.30 (3H, m), 2.74–2.86 (1H, m), 2.90–3.20 (2H, m), 3.25–3.40 (1H, m), 3.42–3.68 (2H, m), 3.80 (3H, s), 3.85–4.00 (1H, m), 4.24 (1H, dd, J=7.8, 14.1Hz), 4.62 (1H, dd, J=5.7, 14.1Hz), 5.12 (1H, d, J=12.3Hz), 5.32 (1H, d, J=12.3Hz), 6.72–7.03 (8H, m), 7.12 (2H, d, J=8.4Hz), 7.18–7.25 (1H, m)

15 [Example 2]

(R)-8-Fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine hydrochloride:

(R)-8-Fluoro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the same manner as  
20 that in Example 1 except that 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was replaced with 8-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine. Light yellow solid. Yield: 19 %.

E S I / M a s s : 4 3 3 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.58–1.88 (4H, m), 2.22–2.30 (1H, m), 2.48–2.58 (1H, m),  
25 2.68–2.82 (3H, m), 2.99–3.08 (1H, m), 3.21–3.36 (2H, m), 3.81 (3H, s),



4.00-4.05 (1H, m), 5.20 (1H, d, J=13.0Hz), 5.34 (1H, d, J=13.0Hz),  
6.47-6.50 (2H, m), 6.79-6.93 (3H, m), 7.02-7.18 (4H, m), 7.26-7.34 (2H, m)

The obtained product was treated with 4 M hydrochloric acid /  
dioxane in the same manner as that in Example 1 to obtain the title  
5 compound in the form of a brown solid. Yield: 81 %.

E S I / M a s s : 433 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.90-2.32 (4H, m), 2.75-2.88 (1H, m), 2.94-3.23 (2H, m),  
3.28-3.60 (3H, m), 3.81 (3H, s), 3.91-4.00 (1H, m), 4.14-4.30 (1H, m),  
4.58-4.73 (1H, m), 5.17 (1H, d, J=13.0Hz), 5.34 (1H, d, J=13.0Hz),  
10 6.50-6.60 (2H, m), 6.81-7.00 (3H, m), 7.08-7.39 (6H, m)

[Example 3]

(R)-2-Chloro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-yl-  
methyl]dibenzo[b,e][1,4]oxazepine hydrochloride:

(R)-2-Chloro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-  
15 ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the same manner as  
that in Example 1 except that 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]-  
oxazepine was replaced with 2-chloro-5,11-dihydrodibenzo[b,e][1,4]-  
oxazepine. Light yellow solid. Yield: 44 %.

E S I / M a s s : 449 [M+H<sup>+</sup>]

20 NMR (CDCl<sub>3</sub>) δ : 1.60-1.87 (4H, m), 2.20-2.28 (1H, m), 2.48-2.56 (1H, m),  
2.67-2.82 (3H, m), 2.93-3.06 (1H, m), 3.16-3.23 (1H, m), 3.34 (1H, dd,  
J=10.3, 14.7Hz), 3.81 (3H, s), 4.04 (1H, dd, J=4.0, 14.7Hz), 5.15 (1H, d,  
J=13.0Hz), 5.25 (1H, J=13.0Hz), 6.75-6.89 (5H, m), 6.97-7.04 (2H, m),  
7.10-7.16 (2H, m), 7.22-7.30 (2H, m)

25 The obtained product was treated with 4 M hydrogen chloride /

dioxane in the same manner as that in Example 1 to obtain the title compound in the form of a brown solid. Yield: 90 %.

E S I / M a s s : 4 4 9 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.92-2.28(4H, m), 2.72-2.88(1H, m), 2.93-3.13(2H, m),  
5 3.26-3.38(1H, m), 3.43-3.6. (2H, m), 3.81(3H, s), 3.83-3.98(1H, m),  
4.20-4.35(1H, m), 4.61-4.74(1H, m), 5.11(1H, d, J=14.0Hz), 5.27(1H, d,  
J=14.0Hz), 6.87-6.92(5H, m), 7.01-7.16(3H, m), 7.22-7.30(3H, m)

[Example 4]

(R)-3-Chloro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-yl-  
10 methyl]dibenzo[b,e][1,4]oxazepine hydrochloride:

(R)-3-Chloro-5,11-dihydro-5-[1-(4-methoxyphenethyl)pyrrolidin-2-  
ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the same manner as  
that in Example 1 except that 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]-  
oxazepine was replaced with 3-chloro-5,11-dihydrodibenzo[b,e][1,4]-  
15 oxazepine. Light yellow solid. Yield: 55 %.

E S I / M a s s : 4 4 9 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.60-1.90(4H, m), 2.22-2.30(1H, m), 2.52-2.62(1H, m),  
2.68-2.82(3H, m), 2.97-3.07(1H, m), 3.16-3.22(1H, m), 3.35(1H, dd,  
J=10.3, 14.7Hz), 3.81(3H, s), 4.03(1H, dd, J=4.0, 14.7Hz), 5.20(1H, d,  
20 J=13.7Hz), 5.23(1H, d, J=13.7Hz), 6.75-6.90(5H, m), 6.96-7.02(2H, m),  
7.10-7.20(4H, m)

The obtained product was treated with 4 M hydrogen chloride /  
dioxane in the same manner as that in Example 1 to obtain the title  
compound in the form of a brown solid. Yield: 86 %.

25 E S I / M a s s : 4 4 9 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.92-2.03 (1H, m), 2.10-2.30 (3H, m), 2.75-2.84 (1H, m),  
2.96-3.12 (2H, m), 3.24-3.34 (1H, m), 3.44-3.60 (2H, m), 3.81 (1H, s), 3.87-  
3.98 (1H, m), 4.24 (1H, dd, J=8.7, 15.3 Hz), 4.62 (1H, dd, J=6.3, 15.3 Hz),  
5.12 (1H, d, J=14.0 Hz), 5.35 (1H, d, J=14.0 Hz), 6.83-6.96 (3H, m),  
5 6.84 (2H, d, J=9.3 Hz), 7.01-7.19 (4H, m), 7.12 (2H, d, J=9.3 Hz)

[Example 5]

(R)-7-Chloro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)pyrrolidin-  
2-ylmethyl]dibenzo[b,e][1,4]oxazepine hydrochloride:

(R)-3-Chloro-1-[1-(3,4-methylenedioxyphenethyl)piperidine]:

10 (R)-2-Hydroxymethylpyrrolidine (505 mg, 5.00 mmol), 3,4-  
methylenedioxyphenethyl mesylate (1.34 g, 5.50 mmol), sodium carbonate  
(585 mg, 5.50 mmol) and sodium iodide (50 mg, 0.33 mmol) were added to  
acetonitrile (50 ml), and they were heated at 90°C under reflux for 13.5  
hours. The solvent was evaporated under reduced pressure, and the  
15 residue was distributed into ethyl acetate and saturated aqueous sodium  
hydrogencarbonate solution. The organic layer was washed with water  
and then dried over magnesium sulfate. The solvent was evaporated  
under reduced pressure. The obtained residue was dissolved in 25 ml of  
dichloromethane. 712 mg (5.5 mmol) of diisopropylethylamine and 630  
20 mg (5.5 mmol) of methanesulfonyl chloride were added to the obtained  
solution under stirring under cooling with water. They were stirred  
under cooling with ice for 1 hour and then at room temperature for 2  
hours. The reaction mixture was distributed into dichloromethane and  
saturated aqueous sodium hydrogencarbonate solution. The organic  
25 layer was dried over magnesium sulfate and the solvent was evaporated  
under reduced pressure. The residue was subjected to the silica gel

column chromatography. After the elution with hexane and ethyl acetate (15:1) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-3-chloro-1-(3,4-methylenedioxyphenethyl)piperidine in the form of a light yellow oily substance (1.02 g, 76 %).

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.55-1.68 (3H, m), 1.75-1.87 (1H, m), 2.12-2.20 (2H, m), 2.55-2.64 (2H, m), 2.69-2.78 (3H, m), 3.08-3.18 (1H, m), 3.98-4.06 (1H, m), 5.93 (2H, s), 6.63-6.75 (3H, m)

(R)-7-Chloro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)piperidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine:

60 % sodium hydride (48 mg, 1.2 mmol) was washed with hexane in argon gas stream and then suspended in dimethyl sulfoxide (8 ml). The obtained suspension was stirred at room temperature for 30 minutes. 7-Chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine (232 mg, 1 mmol) was added to the suspension, and they were stirred at room temperature for 30 minutes and then at 50°C for 30 minutes. A solution of (R)-3-chloro-1-(3,4-methylenedioxyphenethyl)piperidine (308 mg, 1.15 mmol) in dimethyl sulfoxide (3 ml) was added dropwise to the obtained solution, and they were stirred at 50°C for 4 hours. The reaction mixture was distributed into saturated aqueous sodium hydrogencarbonate solution and ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (10:1) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-7-chloro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)pyrrolidin-2-yl-

methyl]-dibenzo[b,e][1,4]oxazepine in the form of a light yellow solid (362 mg, 78 %).

E S I / M a s s : 4 6 3 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.60-1.84 (4H, m), 2.20-2.30 (1H, m), 2.49-2.59 (1H, m),  
5 2.65-2.78 (3H, m), 2.95-3.05 (1H, m), 3.13-3.21 (1H, m), 3.34 (1H, dd, J=10.3,  
13.0 Hz), 4.00 (1H, dd, J=3.3, 13.0 Hz), 5.15 (1H, d, J=13.0 Hz), 5.23 (1H,  
d, J=13.0 Hz), 5.95 (2H, s), 6.63-6.78 (5H, m), 6.96 (1H, s), 7.02-7.13 (2H,  
m), 7.26-7.37 (2H, m)

(R)-7-Chloro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)pyrrolidin-  
10 2-ylmethyl]dibenzo[b,e][1,4]oxazepine hydrochloride:

3.0 ml of 2 M hydrogen chloride / diethyl ether was added to a  
solution of (R)-7-chloro-5,11-dihydro-5-[1-(3,4-methylenedioxyphenethyl)-  
pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine (0.63 g) in dichloro-  
methane (5 ml), and they were stirred together for 2 hours. The solvent  
15 was evaporated under reduced pressure. The obtained residue was  
stirred in hexane to obtain the title compound in the form of a light brown  
solid (348 mg, 89 %).

E S I / M a s s : 4 6 3 [M + H<sup>+</sup>]

20 N M R (C D C l 3 )  $\delta$  : 1.92-2.33 (4H, m), 2.74-3.16 (3H, m), 3.24-3.37 (1H, m),  
3.44-3.58 (2H, m), 3.88-3.98 (1H, m), 4.15-4.28 (1H, m), 4.60-4.72 (1H, m),  
5.19 (1H, d, J=14.0 Hz), 5.27 (1H, d, J=14.0 Hz), 5.98 (2H, s), 6.64-6.77 (5H,  
m), 6.80-6.88 (1H, m), 6.98 (1H, s), 7.09-7.20 (2H, m), 7.28-7.38 (2H, m)

[Example 6]

25 (R)-1-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-  
yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-2-Hydroxymethyl-1-(4-dimethylaminophenethyl)pyrrolidine:

D-Prolinol (2.02 g, 20.0 mmol), 4-dimethylaminophenethyl mesylate (5.35 g, 22.0 mmol), sodium carbonate (2.65 g, 25.0 mmol) and sodium iodide (300 mg, 2.0 mmol) were added to acetonitrile (50 ml), and  
5 they were heated at 90°C under reflux for 13.5 hours. The reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated to dryness under reduced pressure, and the residue was distributed into ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. 1 M hydrochloric acid was added to the  
10 organic layer and pH of the aqueous layer was kept at 1 to extract the intended product in the aqueous layer. 4 M sodium hydroxide was added to the aqueous layer to adjust pH of the aqueous layer to 14, and the precipitates thus formed were extracted with ethyl acetate. The extract was dried over magnesium sulfate, and the solvent was evaporated under  
15 reduced pressure to obtain (R)-2-hydroxymethyl-1-(4-dimethylaminophenethyl)pyrrolidine in the form of a light yellow oily substance (4.91 g, 99 %).

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.69–1.90 (4H, m), 2.29–2.38 (1H, m), 2.45–2.54 (1H, m),  
2.56–2.64 (1H, m), 2.66–2.74 (2H, m), 2.88–2.94 (1H, m), 2.91 (6H, ms),  
20 3.23–3.30 (1H, m), 3.31 (1H, dd, J=2.7, 12.0 Hz), 3.58 (1H, dd, J=4.0, 12.0 Hz), 6.70 (2H, d, J=9.7 Hz), 7.07 (2H, d, J=9.7 Hz)

(R)-3-Chloro-1-(4-dimethylaminophenethyl)piperidine:

(R)-2-Hydroxymethyl-1-(4-dimethylaminophenethyl)pyrrolidine (4.91 g, 19.8 mmol) was dissolved in 60 ml of dichloromethane. 3.11 g  
25 (24.4 mmol) of diisopropylethylamine and 2.75 g (24.0 mmol) of methanesulfonyl chloride were added to the obtained solution under

stirring under cooling with ice. They were stirred under cooling with ice for 1 hour and then at room temperature for 2 hours. The reaction mixture was distributed into dichloromethane and saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried over  
5 magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (9:1) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-3-chloro-1-(4-  
10 dimethylaminophenethyl)piperidine in the form of a light yellow solid (3.03 g, 57 %).

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.50-1.68 (3H, m), 1.76-1.88 (1H, m), 2.09-2.20 (2H, m), 2.55-2.62 (2H, m), 2.66-2.73 (2H, m), 2.75-2.84 (1H, m), 2.91 (6H, s), 3.08-3.17 (1H, m), 3.98-4.08 (1H, m), 6.69 (2H, d, J=9.7Hz), 7.06 (2H, d,  
15 J=9.7Hz)

(R)-1-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine:

60 % sodium hydride (35 mg, 0.88 mmol) was washed with hexane in argon stream and then suspended in dimethyl sulfoxide (5 ml), and the  
20 obtained suspension was stirred at room temperature for 30 minutes. 1-Fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine (0.17 g, 0.80 mmol) was added to the suspension, and they were stirred at room temperature for 30 minutes and then at 50°C for additional 30 minutes. A solution of (R)-3-chloro-1-(4-dimethylaminophenethyl)piperidine (0.18 g, 0.80 mmol)  
25 in dimethyl sulfoxide (2 ml) was added dropwise to the obtained solution, and they were stirred at 50°C for 6 hours. The reaction mixture was

distributed into saturated aqueous sodium chloride solution and ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (6:4) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-1-fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)piperidin-2-ylmethyl]dibenzo[b,e][1,4]-oxazepine in the form of a light yellow oily substance (0.23 g, 64 %).

E S I / M a s s : 4 4 6 [M + H<sup>+</sup>]

10 NMR (CDCl<sub>3</sub>)  $\delta$  : 1.60-1.90 (4H, m), 2.20-2.30 (1H, m), 2.48-2.55 (1H, m), 2.70-2.80 (3H, m), 2.94 (6H, s), 2.98-3.08 (1H, m), 3.16-3.25 (1H, m), 3.38 (1H, dd, J=9.3, 13.0Hz), 4.10 (1H, dd, J=3.60, 13.0Hz), 5.35 (1H, d, J=12.0Hz), 5.42 (1H, d, J=12.0Hz), 6.70-6.78 (3H, m), 6.80-6.90 (4H, m), 7.00-7.15 (3H, m), 7.18-7.28 (1H, m)

15 (R)-1-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

0.5 ml of 4 M hydrogen chloride / dioxane was added to a solution of (R)-1-fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine in dichloromethane (5 ml), and they were stirred together for 30 minutes. The solvent was evaporated under reduced pressure. The obtained residue was solidified with a mixed solvent of hexane and ethyl acetate. The solid thus precipitated was taken by the filtration to obtain the title compound in the form of a brown solid (170 mg, 64 %).

25 E S I / M a s s : 4 4 6 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.92-2.30 (3H, m), 2.78-2.90 (1H, m), 2.91-3.16 (3H, m),



3.16(6H, s), 3.38-3.50(2H, m), 3.62-3.75(1H, m), 3.82-3.95(1H, m),  
4.28(1H, dd, J=6.3, 14.7Hz), 4.77(1H, dd, J=6.0, 14.7Hz), 5.24(2H, s),  
6.76(1H, t, J=8.1Hz), 6.90-7.12(5H, m), 7.21-7.30(1H, m), 7.37(2H, d,  
J=8.4Hz) , 7.71(2H, d, J=8.4Hz)

5 [Example 7]

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the  
10 form of a light yellow oily substance in the same manner as that in  
Example 6 except that 1-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine  
was replaced with 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine.  
(0.24 g, 53 %).

E S I / M a s s : 4 4 6 [M+H<sup>+</sup>]

15 NMR (CDCl<sub>3</sub>) δ : 1.60-1.90(4H, m), 2.22-2.32(1H, m), 2.50-2.60(1H, m),  
2.70-2.82(3H, m), 2.94(6H, s), 2.98-3.08(1H, m), 3.15-3.25(1H, m),  
3.34(1H, dd, J=9.3, 13.0Hz), 4.05(1H, dd, J=3.60, 13.0Hz), 5.20(1H, d,  
J=12.0Hz), 5.26(1H, d, J=12.0Hz), 6.68-6.90(7H, m), 6.97-7.04(1H, m),  
7.08-7.15(2H, m), 7.20-7.25(1H, m)

20 The obtained product was treated with 4 M hydrogen chloride /  
dioxane in the same manner as that in Example 6 to obtain the title  
compound in the form of a light brown solid (100 %)

E S I / M a s s : 4 4 6 [M+H<sup>+</sup>]

25 NMR (CDCl<sub>3</sub>) δ : 1.95-2.30(3H, m), 2.80-3.00(1H, m), 3.00-3.25(9H, m),  
3.42-3.60(2H, m), 3.60-3.75(1H, m), 3.85-3.98(1H, m), 4.19-4.28(1H, m),

4.58-4.68 (1H, m), 5.11 (1H, d, J=12.6Hz), 5.35 (1H, d, J=12.6Hz), 6.76 (1H, t, J=8.1Hz), 6.80-7.08 (5H, m), 7.20 (1H, dd, J=6.3, 8.1Hz), 7.43 (2H, d, J=6.9Hz), 7.75 (2H, d, J=6.9Hz)

[Example 8]

5 (R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the same manner as that in Example 6 except that 1-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was replaced with 3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine. Light yellow oily substance. Yield: 67 %.

E S I / M a s s : 4 6 2 [M+H<sup>+</sup>]

15 NMR (CDCl<sub>3</sub>)  $\delta$  : 1.50-1.91 (4H, m), 2.23-2.32 (1H, m), 2.51-2.60 (1H, m), 2.65-2.83 (3H, m), 2.93 (6H, s), 2.97-3.07 (1H, m), 3.15-3.23 (1H, m), 3.34 (1H, dd, J=10.3, 14.3Hz), 4.06 (1H, dd, J=4.0, 14.3Hz), 5.22 (2H, s), 6.72 (2H, d, J=10.0Hz), 6.75-6.85 (3H, m), 6.98-7.01 (2H, m), 7.09-7.19 (2H, m), 7.11 (2H, d, J=10.0Hz)

(R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine (306 mg, 0.662 mmol) was dissolved in 6.0 ml of a mixed solvent of ethyl acetate and ethanol (2:1). 2 M hydrogen chloride / ether (0.73 ml, 1.46 mmol) was added to the obtained solution. 2.0 ml of ethyl acetate was added to the mixture and they were stirred at room temperature. After leaving the reaction mixture to stand at room temperature for 2 days followed by the filtration and drying, the title compound was obtained in the form of white crystals

(96 %).

E S I / M a s s : 4 6 2 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>)  $\delta$  : 2.02–2.28 (4H, m), 2.80–2.90 (1H, m), 2.98–3.24 (2H, m),  
3.17 (6H, s), 3.44–3.56 (2H, m), 3.59–3.69 (1H, m), 3.88–3.98 (1H, m),  
5 4.23 (1H, dd, J=7.7, 15.7Hz), 4.64 (1H, dd, J=6.3, 15.7Hz), 5.11 (1H, d,  
J=14.0Hz), 5.33 (1H, d, J=14.0Hz), 6.85–6.97 (3H, m), 7.02–7.07 (2H, m),  
7.12–7.18 (2H, m), 7.41 (2H, d, J=9.3Hz), 7.75 (2H, d, J=9.3Hz)

[Example 9]

(R)-2-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-  
10 methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

4-Pyrrolidinophenethyl alcohol:

A solution of 2-(4-bromophenethoxy)tetrahydro-2H-pyran (28.01 g,  
98.39 mmol) in toluene (100 ml) and pyrrolidine (9.93 ml, 119 mmol) were  
added to a mixture of dry palladium acetate (270 mg, 1.20 mmol), 2-(di-t-  
15 butylphosphino)biphenyl (720 mg, 2.40 mmol) and sodium t-butoxide  
(14.42 g, 150 mmol), and they were stirred at 70°C for 12 hours. Water  
was added to the reaction mixture. After the extraction with ethyl  
acetate, the product was extracted from the organic layer with 1 M  
hydrochloric acid. The aqueous layer was neutralized with an aqueous  
20 sodium hydroxide solution and extracted with ethyl acetate. The organic  
layer was dried to obtain 4-pyrrolidinophenethyl alcohol in the form of a  
light yellow solid (16.41 g, 87 %).

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.97–2.01 (4H, m), 2.77 (2H, t, J=7.3Hz), 3.24–3.29 (4H,  
m), 3.79 (2H, q, J=6.7Hz), 6.53 (2H, d, J=9.3Hz), 7.03 (2H, d, J=9.35Hz)

25 4-Pyrrolidinophenethyl mesylate:

4-Pyrrolidinophenethyl alcohol (16.41 g, 85.9 mmol) was dissolved

in dichloromethane (150 ml). Diisopropylethylamine (19.0 ml, 108 mmol) and methanesulfonyl chloride (8.40 ml, 108 mmol) were added to the obtained solution at 0°C, and they were stirred overnight. The reaction mixture was distributed into 5 % aqueous sodium hydrogencarbonate solution and dichloromethane. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (7:3) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain 4-pyrrolidinophenethyl mesylate in the form of a white solid (21.14 g, 80 %).

E S I / M a s s : 2 7 0 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.98-2.01 (4H, m), 2.84 (3H, s), 2.95 (2H, t, J=8.0Hz), 3.24-3.28 (4H, m), 4.46 (2H, t, J=8.0Hz), 6.52 (2H, d, J=9.3Hz), 7.07 (2H, d, J=9.3Hz)

(R)-2-Hydroxymethyl-1-(4-pyrrolidinophenethyl)pyrrolidine:

D-Prolinol (2.72 g, 25.0 mmol), 4-pyrrolidinophenethyl mesylate (6.06 g, 22.5 mmol) and sodium carbonate (3.45 g, 25.0 mmol) were added to acetonitrile (150 ml), and they were heated at 90°C under reflux for 3.5 hours. The reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated to dryness under reduced pressure, and the residue was distributed into ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. 1 M hydrochloric acid was added to the organic layer and pH of the aqueous layer was kept at 1 to extract the intended product in the aqueous layer. 4 M sodium hydroxide was added to the aqueous layer to adjust pH of the

aqueous layer to 14, and the intended product was extracted from the precipitates thus formed with ethyl acetate. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain (R)-2-hydroxymethyl-1-(4-pyrrolidinophenethyl)-pyrrolidine in the form of a light yellow oily substance (4.96 g, 85 %).

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.70-1.91 (4H, m), 1.95-2.04 (4H, m), 2.26-2.36 (1H, m), 2.42-2.56 (1H, m), 2.57-2.77 (4H, m), 2.87-2.96 (1H, m), 3.18-3.27 (4H, m), 3.28 (1H, dd, J=2.7, 12.0Hz), 3.57 (1H, dd, J=4.0, 12.0Hz), 6.51 (2H, d, J=9.3Hz), 7.05 (2H, d, J=9.7Hz)

10 (R)-3-Chloro-1-(4-pyrrolidinophenethyl)piperidine:

(R)-2-Hydroxymethyl-1-(4-pyrrolidinophenethyl)pyrrolidine (4.96 g, 19.1 mmol) was dissolved in 70 ml of dichloromethane. 3.21 g (24.8 mmol) of diisopropylethylamine and 2.84 g (24.8 mmol) of methanesulfonyl chloride were added to the obtained solution under stirring under cooling with ice. They were stirred under cooling with ice for 1 hour and then at room temperature for 2 hours. The reaction mixture was distributed into dichloromethane and saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (3:1) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-3-chloro-1-(4-pyrrolidinophenethyl)piperidine in the form of a light yellow solid (3.23 g, 61 %).

E S I / M a s s : 2 9 3 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.50–1.70 (3H, m), 1.78–1.87 (1H, m), 1.96–2.01 (4H, m), 2.10–2.20 (2H, m), 2.54–2.61 (2H, m), 2.65–2.72 (2H, m), 2.75–2.85 (1H, m), 3.10–3.17 (1H, m), 3.23–3.28 (4H, m), 3.96–4.06 (1H, m), 6.51 (2H, d, J=9.7Hz), 7.05 (2H, d, J=9.7Hz)

5 (R)-2-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine:

60 % sodium hydride (348 mg, 8.7 mmol) was washed with hexane in argon stream and then suspended in dimethyl sulfoxide (50 ml), and the obtained suspension was stirred at room temperature for 30 minutes.

10 2-Fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine (1.70 g, 7.90 mmol) was added to the suspension, and they were stirred at room temperature for 30 minutes and then at 50°C for additional 30 minutes. A solution of (R)-3-chloro-1-(4-pyrrolidinophenethyl)piperidine (2.64 g, 9.02 mmol) in dimethyl sulfoxide (25 ml) was added dropwise to the obtained solution, 15 and they were stirred at 50°C for 3 hours. The reaction mixture was distributed into saturated aqueous sodium hydrogencarbonate solution and ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and 20 ethyl acetate (6:1) and then with hexane and ethyl acetate (1:1) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-2-fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine in the form of a light yellow oily substance (2.29 g, 68 %).

25 ESI / Mass : 472 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.59–1.86 (4H, m), 1.96–2.02 (4H, m), 2.21–2.29 (1H, m),

2.46-2.55 (1H, m), 2.60-2.78 (3H, m), 2.97-3.06 (1H, m), 3.19-3.31 (6H, m),  
4.08 (1H, dd, 3.7, 14.3 Hz), 5.16 (1H, m), 5.30 (1H, d, J=13.0 Hz),  
6.54 (2H, d, J=9.0 Hz), 6.75-6.85 (3H, m), 6.95-7.09 (4H, m),  
6.99 (2H, d, J=9.0 Hz)

5 (R)-2-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

20 ml of 2 M hydrogen chloride / diethyl ether was added to a solution of (R)-2-fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine (2.29 g) in  
10 dichloromethane (30 ml), and they were stirred together for 2 hours. The solvent was evaporated under reduced pressure. The obtained residue was solidified by stirring it in hexane. The solid thus precipitated was taken by the filtration to obtain the title compound in the form of a brown solid (2.17 g, 81 %).

15 E S I / M a s s : 4 7 2 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.95-2.36 (8H, m), 2.84-2.96 (1H, m), 3.03-3.27 (3H, m),  
3.40-3.72 (6H, m), 3.82-3.93 (1H, m), 4.21 (1H, dd, J=8.7, 15.7 Hz), 4.63 (1H,  
dd, J=6.3, 15.7 Hz), 5.13 (1H, d, J=14.0 Hz), 5.33 (1H, d, J=14.0 Hz),  
6.81-7.03 (6H, m), 7.11-7.14 (1H, m), 7.37 (2H, d, J=9.0 Hz), 7.60 (2H, d,  
20 J=9.0 Hz)

[Example 10]

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-  
25 2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the form of a light yellow oily substance (0.19 g, 50 %) in the same manner as that in

Example 6 except that 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine and (R)-3-chloro-1-(4-pyrrolidinophenethyl)piperidine were used.

E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.55-1.90 (4H, m), 1.95-2.06 (4H, m), 2.20-2.32 (1H, m), 2.48-2.60 (1H, m), 2.70-2.82 (3H, m), 2.95-3.10 (1H, m), 3.18-3.40 (6H, m), 4.06 (1H, m), 5.20 (1H, d, J=12.0Hz), 5.26 (1H, d, J=12.0Hz), 6.54 (2H, d, J=8.7Hz), 6.68-6.85 (5H, m), 6.95-7.03 (1H, m), 7.08 (2H, d, J=8.7Hz), 7.20-7.30 (1H, m)

The obtained product was treated with 4 M hydrogen chloride / dioxane in the same manner as that in Example 6 to obtain the title compound in the form of a brown solid (90 %).

E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.95-2.30 (4H, m), 2.34 (4H, m), 2.82-2.95 (1H, m), 3.00-3.24 (2H, m), 3.39-3.78 (7H, m), 3.82-3.95 (1H, m), 4.21 (1H, dd, J=7.2, 14.1Hz), 4.62 (1H, dd, J=5.7, 14.1Hz), 5.11 (1H, d, J=12.6Hz), 5.34 (1H, d, J=12.6Hz), 6.76 (1H, t, J=8.1Hz), 6.80-7.05 (5H, m), 7.19 (1H, t, J=8.1Hz), 7.37 (2H, d, J=8.4Hz), 7.64 (2H, d, J=8.4Hz)

[Example 11]

(R)-7-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-7-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the form of a light yellow oily substance (0.19 g, 51 %) in the same manner as that in Example 6 except that 7-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine and (R)-3-chloro-1-(4-pyrrolidinophenethyl)piperidine were used.



E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.58-1.90 (4H, m), 1.95-2.06 (4H, m), 2.20-2.32 (1H, m),  
2.48-2.60 (1H, m), 2.68-2.82 (3H, m), 2.98-3.08 (1H, m), 3.18-3.40 (6H, m),  
4.05 (1H, dd, J=5.8, 13.2 Hz), 5.14 (1H, d, J=12.0 Hz), 5.31 (1H, d,  
5 J=12.0 Hz), 6.45-6.58 (3H, m), 6.68-6.78 (2H, m), 7.02-7.13 (4H, m),  
7.28-7.35 (2H, m)

The obtained product was treated with 4 M hydrogen chloride /  
dioxane in the same manner as that in Example 6 to obtain the title  
compound in the form of a brown solid (98 %).

10 E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.95-2.30 (4H, m), 2.34 (4H, m), 2.78-2.92 (1H, m),  
2.94-3.25 (2H, m), 3.40-3.76 (7H, m), 3.83-3.94 (1H, m), 4.23 (1H, dd, J=7.2,  
14.4 Hz), 4.66 (1H, dd, J=6.0, 14.4 Hz), 5.13 (1H, d, J=12.9 Hz), 5.24 (1H,  
d, J=12.9 Hz), 6.58-6.63 (1H, m), 6.72-6.82 (2H, m), 7.05-7.25 (4H, m),  
15 7.35 (2H, d, J=8.4 Hz), 7.60 (2H, d, J=8.4 Hz)

[Example 12]

(R)-8-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-  
methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-8-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-  
20 2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the form of a light  
yellow oily substance (0.13 g, 32 %) in the same manner as that in  
Example 6 except that 8-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine  
and (R)-3-chloro-1-(4-pyrrolidinophenethyl)piperidine were used.

E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

25 N M R (C D C l 3 )  $\delta$  : 1.58-1.90 (4H, m), 1.95-2.06 (4H, m), 2.18-2.34 (1H, m),

2.45-2.58(1H, m), 2.65-2.80(3H, m), 2.95-3.10(1H, m), 3.14-3.38(6H, m),  
4.05-4.14(1H, m), 5.21(1H, d, J=11.7Hz), 5.35(1H, d, J=11.7Hz),  
6.48-6.58(4H, m), 6.88-6.95(1H, m), 7.02-7.12(4H, m), 7.24-7.35(2H, m)

The obtained product was treated with 4 M hydrogen chloride /  
5 dioxane in the same manner as that in Example 6 to obtain the title  
compound in the form of a brown solid (98 %).

E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

N M R (C D C l 3 ) δ : 1.95-2.30(4H, m), 2.35(4H, m), 2.78-2.94(1H, m),  
2.95-3.10(1H, m), 3.10-3.25(1H, m), 3.40-3.80(7H, m), 3.80-3.95(1H, m),  
10 4.19(1H, dd, J=7.8, 14.1Hz), 4.64(1H, dd, J=4.2, 14.1Hz), 5.16(1H, d,  
J=12.3Hz), 5.44(1H, d, J=12.3Hz), 6.50-6.61(2H, m), 6.88-7.00(1H, m),  
7.05-7.18(2H, m), 7.30-7.41(4H, m), 7.64(2H, d, J=7.8Hz)

[Example 13]

(R)-3-Chloro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-  
15 methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Chloro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)-  
pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained in the  
form of a light yellow oily substance (0.18 g, 68 %) in the same manner as  
that in Example 6 except that 3-chloro-5,11-dihydrodibenzo[b,e][1,4]-  
20 oxazepine and (R)-3-chloro-1-(4-pyrrolidinophenethyl)piperidine were  
used.

E S I / M a s s : 4 8 8 [M + H<sup>+</sup>]

N M R (C D C l 3 ) δ : 1.50-1.90(4H, m), 1.95-2.06(4H, m), 2.20-2.34(1H, m),  
2.50-2.62(1H, m), 2.65-2.82(3H, m), 2.90-3.10(1H, m), 3.16-3.40(6H, m),  
25 4.05-4.14(1H, m), 5.22(2H, s), 6.54(2H, d, J=8.7Hz), 6.75-6.88(3H, m),

6.96-7.04(2H, d, J=8.7Hz), 7.05-7.14(3H, m), 7.18(1H, d, J=8.4Hz)

The obtained product was treated with 4 M hydrogen chloride / dioxane in the same manner as that in Example 6 to obtain the title compound in the form of a brown solid (91 %).

5 E S I / M a s s : 4 8 8 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.95-2.30(4H, m), 2.34(4H, m), 2.78-2.92(1H, m),  
2.92-3.25(2H, m), 3.40-3.81(7H, m), 3.83-3.99(1H, m), 4.21(1H, dd, J=6.9,  
14.1Hz), 4.63(1H, dd, J=6.3, 14.1Hz), 5.10(1H, d, J=12.9Hz), 5.36(1H,  
d, J=12.9Hz), 6.85-7.06(5H, m), 7.15(2H, t, J=8.1Hz), 7.35(2H, d,  
10 J=8.7Hz), 7.62(2H, d, J=8.7Hz)

[Example 14]

(R)-3-Chloro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-yl-  
methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

3-Pyrrolidinophenethyl alcohol:

15 A solution of 2-(3-bromophenethoxy)tetrahydro-2H-pyran (6.27 g,  
21.9 mmol) in toluene (15 ml) and pyrrolidine (2.2 ml, 26.4 mmol) were  
added to a mixture of dry palladium acetate (58 mg, 0.26 mmol), 2-(di-t-  
butylphosphino)biphenyl (136 mg, 0.46 mmol) and sodium t-butoxide  
(3.23 g, 33.6 mmol), and they were stirred at 70°C for 12 hours. Water  
20 was added to the reaction mixture. After the extraction with ethyl  
acetate, the product was extracted from the organic layer with 1 M  
hydrochloric acid. The aqueous layer was neutralized with an aqueous  
sodium hydroxide solution and the product was extracted with ethyl  
acetate. The organic layer was dried to quantitatively obtain 3-  
25 pyrrolidinophenethyl alcohol in the form of a light yellow solid.

N M R (C D C l 3 )  $\delta$  : 1.98-2.02(4H, m), 2.82(2H, t, J=7.0Hz), 3.26-3.30(4H,

m), 3.86(2H, q, J=7.0Hz), 6.42-6.54(3H, m), 7.17(1H, t, J=8.3Hz)

### 3-Pyrrolidinophenethyl mesylate:

3-Pyrrolidinophenethyl alcohol was dissolved in dichloromethane (20 ml). Triethylamine (3.7 ml, 26.7 mmol) and methanesulfonyl chloride (1.9 ml, 24.5 mmol) were added to the obtained solution at 0°C, and they were stirred overnight. The reaction mixture was distributed into 5 % aqueous sodium hydrogencarbonate solution and dichloromethane. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (7:3), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain 3-pyrrolidinophenethyl mesylate in the form of a white solid (5.13 g, 87 %).

E S I / M a s s : 270 [M+H<sup>+</sup>]

N M R (CDCl<sub>3</sub>) δ : 1.98-2.03(4H, m), 2.86(3H, s), 2.98(2H, t, J=7.3Hz), 3.25-3.30(4H, m), 4.43(2H, t, J=7.3Hz), 6.40-6.53(3H, m), 7.16(1H, t, J=8.7Hz)

### (R)-3-Chloro-1-(3-pyrrolidinophenethyl)piperidine:

(R)-3-Chloro-1-(3-pyrrolidinophenethyl)piperidine was synthesized in the same manner as that in Example 13 except that 4-pyrrolidinophenethyl mesylate was replaced with 3-pyrrolidinophenethyl mesylate. Yield: 50 %.

E S I / M a s s : 293 [M+H<sup>+</sup>]

N M R (CDCl<sub>3</sub>) δ : 1.55-1.70(2H, m), 1.78-1.88(2H, m), 1.95-2.03(4H, m), 2.10-2.22(2H, m), 2.30(1H, t, J=10.5Hz), 2.60-2.67(2H, m), 2.67-2.82(2H,

m), 3.16(1H, m), 3.22-3.30(4H, m), 4.02(1H, m), 6.40(2H, m), 6.49(1H, d, J=7.5Hz), 7.13(1H, t, J=7.5Hz)

(R)-3-Chloro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine:

5 (R)-3-Chloro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)-pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine was obtained in the form of a light yellow oily substance (0.21 g, 45 %) from 3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine and (R)-3-chloro-1-(3-pyrrolidinophenethyl)piperidine in the same manner as that in Example 6.

10 E S I / M a s s : 4 8 8 [M+H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.50-1.90(4H, m), 1.95-2.06(4H, m), 2.24-2.34(1H, m), 2.55-2.70(1H, m), 2.70-2.88(3H, m), 3.02-3.15(1H, m), 3.16-3.40(6H, m), 4.02-4.14(1H, m), 5.23(2H, s), 6.40-6.58(3H, m), 6.75-6.88(3H, m), 6.96-7.04(2H, m), 7.10-7.20(3H, m)

15 (R)-3-Chloro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

The obtained product was treated with 4 M hydrogen chloride / dioxane in the same manner as that in Example 6 to obtain the title compound in the form of a brown solid (88 %).

20 E S I / M a s s : 4 8 8 [M+H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.95-2.30(4H, m), 2.32(4H, m), 2.77-2.90(1H, m), 3.00-3.30(2H, m), 3.38-3.78(7H, m), 3.80-3.92(1H, m), 4.21(1H, dd, J=6.6, 14.1Hz), 4.64(1H, dd, J=5.7, 14.1Hz), 5.10(1H, d, J=12.9Hz), 5.33(1H, d, J=12.9Hz), 6.82-7.08(5H, m), 7.14(2H, t, J=8.4Hz), 7.20-7.30(1H, m),

25 7.38-7.53(2H, m), 7.60-7.70(1H, m)

[Example 15]

(R)-3-Chloro-5,11-dihydro-5-[1-(4-morpholinophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

4-Morpholinophenethyl alcohol:

5           A solution of 2-(4-bromophenethoxy)tetrahydro-2H-pyran (3.42 g, 12 mmol) in toluene (9.0 ml) and morpholine (1.22 g, 14 mmol) were added to a mixture of dry palladium acetate (32.3 mg, 0.14 mmol), 2-(di-  
10           butylphosphino)biphenyl (86.0 mg, 0.29 mmol) and sodium t-butoxide (1.73 g, 18 mmol), and they were stirred at 70°C for 16 hours. Water was  
15           added to the reaction mixture. After the extraction with ethyl acetate, the product was extracted from the organic layer with 1 M hydrochloric acid. The aqueous layer was neutralized with an aqueous sodium hydroxide solution and the product was extracted with ethyl acetate. The organic layer was dried to obtain 4-morpholinophenethyl alcohol in  
15           the form of a light yellow solid (2.35 g, 95 %).

N M R (CDCl<sub>3</sub>)  $\delta$  : 2.80 (2H, t, J=8.7Hz), 3.13 (4H, t, J=6.8), 3.78-3.88 (6H, m), 6.88 (2H, d, J=11.7Hz), 7.14 (2H, d, J=11.7Hz)

4-Morpholinophenethyl mesylate:

20           4-Morpholinophenethyl alcohol (2.35 g, 11.3 mmol) was dissolved in dichloromethane (20 ml). Diisopropylethylamine (2.60 ml, 14.8 mmol) and methanesulfonyl chloride (1.11 ml, 14.8 mmol) were added to the  
25           obtained solution at 0°C, and they were stirred for 4 hours. The reaction mixture was distributed into 5 % aqueous sodium hydrogencarbonate solution and dichloromethane. The organic layer was dried and the  
25           solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution

with hexane and ethyl acetate (3:1) and then with them (1:1) as the eluents, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain 4-morpholinophenethyl mesylate in the form of a white solid (2.60 g, 81 %).

5 N M R (CDCl<sub>3</sub>)  $\delta$  : 2.86(3H, s), 2.98(2H, t, J=9.3Hz), 3.14(4H, m), 3.86(4H, m), 4.38(2H, t, J=9.3Hz), 6.87(2H, d, J=11.7Hz), 7.14(2H, d, J=11.7Hz)

(R)-3-Chloro-1-(4-morpholinophenethyl)piperidine:

4-Morpholinophenethyl mesylate (0.43 g, 1.51 mmol), D-prolinol  
10 (0.17 g, 1.66 mmol) and sodium carbonate (0.40 g, 2.89 mmol) were added to acetonitrile (20 ml), and they were stirred under heating at 70°C overnight. The reaction mixture was cooled and then filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was distributed into water and ethyl acetate. The intended  
15 product was extracted from ethyl acetate layer with 1 M hydrochloric acid. The aqueous layer was neutralized and the product was again extracted with ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure to obtain (R)-2-hydroxymethyl-1-(4-morpholinophenethyl)pyrrolidine in the form of a light yellow solid (0.44  
20 g, 1.5 mmol, 100 %). This product was dissolved in dichloromethane (10 ml). Triethylamine (0.29 ml, 2.1 mmol) and methanesulfonyl chloride (0.15 ml, 1.9 mmol) were added to the obtained solution at 0°C, and they were stirred at room temperature for 1 hour. The reaction mixture was distributed into 5 % aqueous sodium hydrogencarbonate solution and  
25 dichloromethane. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the

silica gel column chromatography. After the elution with hexane and ethyl acetate (1:1), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-3-chloro-1-(morpholinophenethyl)piperidine in the form of a white solid (0.30 g, 64 %).

E S I / M a s s : 3 0 9 [M+H<sup>+</sup>]

N M R (CDCl<sub>3</sub>) δ : 1.50-1.86(4H, m), 2.10-2.20(2H, m), 2.28(1H, t, J=7.8Hz), 2.55-2.64(2H, m), 2.65-2.80(3H, m), 3.10-3.18(4H, m), 3.80-3.88(4H, m), 3.96-4.04(1H, m), 6.82-6.88(2H, m), 7.10-7.20(2H, m)

(R)-3-Chloro-5,11-dihydro-5-[1-(4-morpholinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Chloro-5,11-dihydro-5-[1-(4-morpholinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine was obtained from (R)-3-chloro-1-(4-morpholinophenethyl)piperidine and 3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine in the same manner as that in Example 6. Light yellow oily substance. Yield: 46 %.

E S I / M a s s : 5 0 4 [M+H<sup>+</sup>]

N M R (CDCl<sub>3</sub>) δ : 1.60-1.95(4H, m), 2.22-2.31(1H, m), 2.52-2.61(1H, m), 2.69-2.80(3H, m), 2.98-3.07(1H, m), 3.01-3.19(1H, m), 3.15(4H, t, J=5.3Hz), 3.35(1H, dd, J=10.3, 14.7Hz), 3.87(4H, t, J=5.3Hz), 4.03(1H, dd, J=4.0, 14.7Hz), 5.21(1H, d, J=13.3Hz), 5.23(1H, d, J=13.3Hz), 6.76-6.90(3H, m), 6.88(2H, d, J=9.7Hz), 6.97-7.01(2H, m), 7.09-7.19(2H, m), 7.14(2H, d, J=9.7Hz)

The obtained product was treated with 4 M hydrogen chloride / dioxane in the same manner as that in Example 6 to obtain the title compound in the form of a brown solid. Yield: 96 %



E S I / M a s s : 5 0 4 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.98-2.33 (4H, m), 2.83-3.30 (4H, m), 3.38-3.70 (6H, m),  
3.87-3.98 (1H, m), 4.15-4.42 (5H, m), 4.60-4.70 (1H, m), 5.12 (1H, d,  
J=14.0 Hz), 5.39 (1H, d, J=14.0 Hz), 6.84-6.93 (3H, m), 7.04-7.19 (4H, m),  
5 7.43 (2H, s), 7.78 (2H, s)

[Example 16]

(R)-2-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-2-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine:  
10

60 % sodium hydride (100 mg, 2.5 mmol) was washed with hexane in argon stream and then suspended in dimethyl sulfoxide (8 ml), and the obtained suspension was stirred at room temperature for 30 minutes. 2-Fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine (538 mg, 2.5 mmol) was  
15 added to the suspension, and they were stirred at room temperature for 30 minutes and then at 50°C for additional 40 minutes. A solution of (S)-1-(4-dimethylaminophenethyl)-3-methanesulfonyloxypyrrolidine (312 mg, 1.0 mmol, prepared by a method disclosed in International Patent No. 0040570A1) in dimethyl sulfoxide (3 ml) was added dropwise to the  
20 obtained solution, and they were stirred at 50°C for 13 hours. The reaction mixture was poured into ice / water and then subjected to the extraction with ethyl acetate. The organic layer was dried and then the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution  
25 with hexane and ethyl acetate (3:1) and then with hexane and ethyl acetate (1:1) as the eluent, suitable fractions were collected and the

solvent was evaporated under reduced pressure to obtain (R)-2-fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine in the form of a light yellow oily substance (140 mg, 32 %).

5 E S I / M a s s : 4 3 2 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.74-1.84(1H, m), 2.22-2.34(1H, m), 2.37-2.47(1H, m), 2.48-2.71(5H, m), 2.75-2.85(1H, m), 2.90(6H, s), 3.18(1H, dd, J=7.7, 10.7Hz), 4.60-4.70(1H, m), 5.25-5.40(2H, bs), 6.37-6.49(3H, m), 6.72-6.87(5H, m), 6.95-7.24(3H, m),

10 (R)-2-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

1.0 ml of 4 M hydrogen chloride / ethyl acetate was added to a solution of (R)-2-fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine (140 mg) in dichloromethane (5  
15 ml), and they were stirred together for 1 hour. The solvent was evaporated under reduced pressure. The obtained residue was solidified by stirring it in hexane and then filtered to obtain the title compound in the form of a light yellow solid (145 mg, 90 %).

E S I / M a s s : 4 3 2 [M + H<sup>+</sup>]

20 NMR (CD<sub>3</sub>OD) δ : 1.90-2.08(1H, m), 2.10-2.30(1H, m), 2.38-2.53(1H, m), 2.60-2.73(1H, m), 3.14(2H, t, J=8.0Hz), 3.26(6H, s), 3.49(2H, t, J=8.0Hz), 3.60-3.82(2H, m), 4.03-4.14(1H, m), 4.95-5.03(1H, m), 5.06-5.15(1H, m), 6.73-6.92(3H, m), 7.03-7.26(4H, m), 7.47-7.59(4H, m)  
[Example 17]

25 (R)-3-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Fluoro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine was obtained in the same manner as that in Example 16 except that 2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was replaced with 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine. Light yellow solid. Yield: 40 %.

E S I / M a s s : 4 3 2 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.73-1.84 (1H, m), 2.21-2.30 (1H, m), 2.41-2.48 (1H, m), 2.50-2.71 (5H, m), 2.75-2.82 (1H, m), 2.90 (6H, s), 3.18 (1H, dd, J=7.7, 10.7Hz), 5.28 (1H, d, J=12.0Hz), 5.40 (1H, d, J=12.0Hz), 6.48-6.54 (1H, m), 6.63-6.72 (4H, m), 7.01-7.12 (4H, m), 7.25-7.34 (2H, m)

The obtained product was treated with 4 M hydrogen chloride / ethyl acetate in the same manner as that in Example 16 to obtain the title compound in the form of a light brown solid. Yield: 92 %.

E S I / M a s s : 4 3 2 [M + H<sup>+</sup>]

NMR (CD<sub>3</sub>OD) δ : 1.90-2.07 (1H, m), 2.14-2.27 (1H, m), 2.42-2.52 (1H, m), 2.63-2.77 (1H, m), 3.15 (2H, t, J=9.0Hz), 3.26 (6H, s), 3.49 (2H, t, J=9.0Hz), 3.64-3.82 (2H, m), 4.07-4.16 (1H, m), 4.97-5.06 (1H, m), 5.10-5.18 (1H, m), 6.72-6.94 (4H, m), 7.00-7.09 (2H, m), 7.43-7.65 (5H, m) [Example 18]

(R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine was obtained in the same manner as that in Example 16 except that 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was replaced with 3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine. Light yellow oily substance. Yield:

39 %.

E S I / M a s s : 4 4 8 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.74-1.84 (1H, m), 2.22-2.34 (1H, m), 2.37-2.47 (1H, m),  
2.48-2.71 (5H, m), 2.75-2.85 (1H, m), 2.90 (6H, s), 3.18 (1H, dd, J=7.7,  
5 10.7Hz), 4.60-4.70 (1H, m), 5.25-5.40 (2H, bs), 6.68 (2H, d, J=9.7Hz),  
6.71-6.88 (4H, m), 6.92-7.10 (3H, m) 7.04 (2H, d, J=9.7Hz)

The obtained product was treated with 4 M hydrogen chloride / ethyl acetate in the same manner as that in Example 16 to obtain the title compound in the form of a brown solid. Yield: 90 %.

10 E S I / M a s s : 4 4 8 [M + H<sup>+</sup>]

NMR (CD<sub>3</sub>OD) δ : 1.86-2.08 (1H, m), 2.10-2.27 (1H, m), 2.40-2.53 (1H, m),  
2.60-2.74 (1H, m), 3.12 (2H, t, J=9.0Hz), 3.27 (6H, s), 3.50 (2H, t, J=9.0Hz),  
3.64-3.84 (2H, m), 4.06-4.16 (1H, m), 5.00-5.08 (1H, m),  
5.10-5.19 (1H, m), 6.73-7.07 (4H, m), 7.17-7.42 (3H, m), 7.47-7.67 (4H, m)

15 [Example 19]

(R)-3-Fluoro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-3-yl]-dibenzo[b,e][1,4]oxazepine dihydrochloride:

(S)-3-Methanesulfonyloxy-1-(3-pyrrolidinophenethyl)pyrrolidine:

3-Pyrrolidinophenethyl mesylate (1.80 g, 4.00 mmol), (S)-3-  
20 pyrrolidinol hydrochloride (0.50 g, 4.05 mmol) and potassium carbonate (1.70 g, 12.3 mmol) were added to acetonitrile (20 ml), and they were stirred at 100°C for 12 hours. Acetonitrile was evaporated under reduced pressure, and the residue was distributed into water and ethyl acetate. The intended product was extracted from the ethyl acetate  
25 layer with 1 M hydrochloric acid. After neutralizing the aqueous layer, the product was again extracted with ethyl acetate. The organic layer

was dried and then the solvent was evaporated under reduced pressure to quantitatively obtain (S)-3-hydroxy-1-(3-pyrrolidinophenethyl)-pyrrolidine in the form of a light yellow solid. This product was dissolved in dichloromethane (10 ml). Triethylamine (0.76 ml, 5.49 mmol) and methanesulfonyl chloride (0.39 ml, 5.03 mmol) were added to the obtained solution at 0°C and they were stirred overnight. The reaction mixture was distributed into 5 % aqueous sodium hydrogencarbonate solution and dichloromethane. The organic layer was dried and then the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with chloroform and methanol (95:5), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-3-methanesulfonyloxy-1-(3-pyrrolidinophenethyl)pyrrolidine in the form of a light yellow oily substance (1.30 g, 96 %).

E S I / M a s s : 3 3 9 [M+H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.99(4H, m), 2.03-2.15(1H, m), 2.25-2.38(1H, m), 2.44-2.54(1H, m); 2.70-2.80(4H, m), 2.80-3.02(3H, m), 3.02(3H, s), 3.23-3.30(4H, m), 5.23(1H, m), 6.42(2H, m), 6.50(1H, d, J=7.5Hz), 7.14(1H, t, J=7.5Hz)

(R)-3-Fluoro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-3-yl]-dibenzo[b,e][1,4]oxazepine:

60 % sodium hydride (88 mg, 2.2 mmol) was washed with hexane in argon gas stream and then suspended in dimethyl sulfoxide (10 ml). The obtained suspension was stirred at room temperature for 30 minutes.

3-Fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine (0.43 g, 2.0 mmol) was added to the suspension, and they were stirred at room temperature for

30 minutes. After stirring at 50°C for 30 minutes, a solution of (S)-3-methanesulfonyloxy-1-(3-pyrrolidinophenethyl)pyrrolidine (0.34 g, 1.0 mmol) in dimethyl sulfoxide (4 ml) was added dropwise to the obtained solution, and they were stirred at 70°C for 2 hours. The reaction mixture  
5 was distributed into saturated aqueous sodium chloride solution and ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (1:1) as the eluent, suitable fractions were collected and the  
10 solvent was evaporated under reduced pressure to obtain (R)-3-fluoro-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo[b,e]-[1,4]oxazepine in the form of a light yellow oily substance (0.19 g, 42 %).

E S I / M a s s : 4 5 8 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.68-1.84 (1H, m), 1.90-1.99 (4H, m), 2.22-2.36 (1H, m),  
15 2.40-2.48 (1H, m), 2.50-2.76 (5H, m), 2.76-2.86 (1H, m), 3.16-3.28 (5H, m),  
4.64 (1H, m), 5.36 (2H, m), 6.37-6.49 (3H, m), 6.72-6.87 (5H, m), 6.95 (1H,  
d, J=6.6Hz), 7.12-7.28 (1H, t, J=7.5Hz), 7.28 (1H, d, J=6.6Hz)

The obtained product was treated with 4 M hydrogen chloride / ethyl acetate in the same manner as that in Example 16 to obtain the title  
20 compound in the form of a brown solid (69 %).

N M R (C D 3 O D )  $\delta$  : 1.90-2.08 (1H, m), 2.10-2.30 (5H, m), 2.35-2.55 (1H, m),  
2.60-2.78 (2H, m), 3.12 (2H, t, J=8.1Hz), 3.30-3.48 (1H, m), 3.53 (1H, t,  
J=8.1Hz), 3.60-3.83 (6H, m), 4.95-5.15 (2H, m), 6.70-7.10 (6H, m),  
7.25-7.53 (5H, m)

25 [Example 20]

(R)-3-Chloro-5,11-dihydro-5-[1-(3-pyrrolidin-1-ylphenethyl)pyrrolidin-3-

yl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-3-Chloro-5,11-dihydro-5-[1-(3-pyrrolidin-1-ylphenethyl)-pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine was obtained in the form of a light yellow oily substance from 3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine and (R)-3-methylsulfonyl-1-(3-pyrrolidin-1-ylphenethyl)pyrrolidine in the same manner as that in Example 19 (0.20 g, 43 %).

E S I / M a s s : 4 7 4 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.63-1.80 (1H, m), 1.92-2.00 (4H, m), 2.22-2.36 (1H, m), 2.40-2.48 (1H, m), 2.52-2.75 (5H, m), 2.75-2.86 (1H, m), 3.15-3.30 (5H, m), 4.60-4.70 (1H, m), 5.38 (2H, brs), 6.37-6.49 (3H, m), 6.72-6.80 (3H, m), 6.95 (1H, dd, J=1.8, 7.8Hz), 7.04-7.14 (3H, m), 7.24 (1H, d, J=7.8Hz)

The obtained product was treated with 4 M hydrogen chloride / ethyl acetate in the same manner as that in Example 16 to obtain the title compound in the form of a brown solid (93 %).

E S I / M a s s : 4 7 4 [M+H<sup>+</sup>]

NMR (CD<sub>3</sub>OD) δ : 1.90-2.10 (1H, m), 2.13-2.32 (5H, m), 2.37-2.55 (1H, m), 2.60-2.78 (2H, m), 3.10 (2H, t, J=7.8Hz), 3.30-3.45 (1H, m), 3.53 (1H, t, J=7.8Hz), 3.58-3.81 (5H, m), 4.00-4.12 (1H, m), 4.95-5.18 (2H, m), 6.70-7.10 (4H, m), 7.16-7.50 (7H, m)

[Example 21]

(R)-5,11-Dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]-dibenzo[b,e][1,4]oxazepine dihydrochloride:

(R)-5,11-Dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]-dibenzo[b,e][1,4]oxazepine:

(R)-5,11-dihydro-5-(2-pyrrolidylmethyl)dibenzo[b,e][1,4]oxazepine

(240 mg, 0.85 mmol, prepared by a method disclosed in International Patent No. 9912925A1), 3-pyrrolidinophenethyl mesylate (253 mg, 0.94 mmol), sodium carbonate (106 mg, 1.0 mmol) and sodium iodide (10 mg, 0.07 mmol) were added to acetonitrile (20 ml), and they were heated at 5 90°C under reflux for 6.5 hours. The solvent was evaporated under reduced pressure, and the residue was distributed into ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with water and then dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained 10 residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (15:1) and then with hexane and ethyl acetate (2:1) as the eluent, suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e]- 15 [1,4]oxazepine in the form of a light yellow oily substance (208 mg, 54 %).

E S I / M a s s : 4 5 4 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.65-1.88 (4H, m), 1.99-2.05 (4H, m), 2.23-2.32 (1H, m), 2.55-2.64 (1H, m), 2.71-2.84 (3H, m), 3.06-3.16 (1H, m), 3.19-3.24 (1H, m), 3.28-3.32 (4H, m), 3.37 (1H, dd, J=11.0, 14.3Hz), 4.15 (1H, dd, J=4.0, 14.3Hz), 5.22 (1H, d, J=13.0Hz), 5.34 (1H, d, J=13.0Hz), 6.44-6.55 (3H, m), 6.75-6.83 (3H, m), 7.00-7.20 (4H, m), 7.26-7.32 (2H, m)

(R)-5,11-Dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]-dibenzo[b,e][1,4]oxazepine dihydrochloride:

2.0 ml of 2 M hydrogen chloride / diethyl ether was added to a 25 solution of (R)-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine (208 mg) in dichloromethane (2 ml),



and they were stirred together for 2 hours. The solvent was evaporated under reduced pressure. The obtained residue was solidified by stirring it in hexane. The solid thus precipitated was taken by the filtration to obtain the title compound in the form of a light brown solid (220 mg, 91 %).

E S I / M a s s : 4 5 4 [M+H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.90-2.42 (8H, m), 2.98-3.30 (3H, m), 3.40-3.90 (8H, m), 4.18-4.35 (1H, m), 4.62-4.76 (1H, m), 5.14 (1H, d, J=13.0Hz), 5.30 (1H, d, J=13.0Hz), 6.78-6.94 (3H, m), 6.97-7.16 (3H, m), 7.20-7.40 (4H, m), 7.45 (1H, s), 7.59 (1H, s)

[Example 22]

(R)-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo-[b,e][1,4]oxazepine dihydrochloride:

(S)-3-Hydroxy-1-(4-pyrrolidinophenethyl)pyrrolidine:

4-Pyrrolidinophenethyl mesylate (13.45 g, 50.0 mmol), (S)-3-pyrrolidinol hydrochloride (5.56 g, 45.0 mmol) and potassium carbonate (18.63 g, 135 mmol) were added to acetonitrile (200 ml), and they were heated at 90°C for 3 hours. The reaction mixture was cooled and then filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was distributed into water and ethyl acetate. The intended product was extracted from the ethyl acetate layer with 1 M hydrochloric acid. The aqueous layer was neutralized and then the product was again extracted with ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure to obtain (S)-3-hydroxy-1-(4-pyrrolidinophenethyl)pyrrolidine in the form of a light yellow solid (6.30 g, 52 %).

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.74-1.84 (1H, m), 1.96-2.04 (4H, m), 2.15-2.25 (1H, m), 2.34-2.43 (1H, m), 2.55-2.63 (1H, m), 2.65-2.80 (5H, m), 2.92-3.03 (1H, m), 3.23-3.28 (4H, m), 4.33-4.40 (1H, m), 6.51 (2H, d, J=9.3Hz), 7.06 (2H, d, J=9.3Hz)

5 (S)-3-Methanesulfonyloxy-1-(4-pyrrolidinophenethyl)pyrrolidine:

(S)-3-Hydroxy-1-(4-pyrrolidinophenethyl)pyrrolidine (6.30 g, 23.4 mmol) was dissolved in 100 ml of dichloromethane. Diisopropylethylamine (5.28 ml, 30.0 mmol) and methanesulfonyl chloride (2.34 ml, 30.0 mmol) were added to the obtained solution at 0°C and they were stirred for 4 hours. The reaction mixture was distributed into 5 % aqueous sodium hydrogencarbonate solution and dichloromethane. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with dichloromethane and methanol (10:1), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (S)-3-methanesulfonyloxy-1-(4-pyrrolidinophenethyl)pyrrolidine in the form of a light yellow oily substance (7.50 g, 49 %).

ESI / Mass : 339 [M+H<sup>+</sup>]

20 NMR (CDCl<sub>3</sub>)  $\delta$  : 1.96-2.00 (4H, m), 2.04-2.16 (1H, m), 2.27-2.38 (1H, m), 2.44-2.52 (1H, m), 2.65-2.74 (4H, m), 2.82-2.98 (3H, m), 3.02 (3H, s), 3.23-3.28 (4H, m), 5.19-5.27 (1H, m), 6.50 (2H, d, J=9.3Hz), 7.05 (2H, d, J=9.3Hz)

(R)-5,11-Dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo-  
25 [b,e][1,4]oxazepine dihydrochloride:

60 % sodium hydride (132 mg, 3.3 mmol) was washed with hexane

in argon stream and then suspended in dimethyl sulfoxide (10 ml), and the obtained suspension was stirred at room temperature for 30 minutes. 5,11-Dihydrodibenzo[b,e][1,4]oxazepine (600 mg, 3.0 mmol) was added to the suspension, and they were stirred at room temperature for 30 minutes  
5 and then at 50°C for additional 30 minutes. A solution of (S)-3-methanesulfonyloxy-1-(4-pyrrolidinophenethyl)pyrrolidine (340 mg, 1.0 mmol) in dimethyl sulfoxide (5 ml) was added dropwise to the obtained solution, and they were stirred at 50°C for 42 hours. The reaction mixture was distributed into saturated aqueous sodium chloride solution  
10 and ethyl acetate. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (3:1), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-5,11-dihydro-5-[1-(4-  
15 pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine in the form of a light yellow oily substance (142 mg, 32 %).

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.72-1.84 (1H, m), 1.96-2.04 (4H, m), 2.22-2.41 (2H, m), 2.49-2.71 (5H, m), 2.80-2.89 (1H, m), 3.22-3.27 (5H, m), 4.67-4.74 (1H, m), 5.30-5.50 (2H, b), 6.48 (2H, d, J=9.7Hz), 6.72-6.82 (3H, m), 6.95-7.13 (3H,  
20 m), 7.02 (2H, d, J=9.7Hz), 7.26-7.33 (2H, m)

The obtained product was treated with 2 M hydrogen chloride / diethyl ether in the same manner as that in Example 21 to obtain the title compound in the form of a brown solid (83 %).

ESI / Mass : 440 [M+H<sup>+</sup>]

25 NMR (CD<sub>3</sub>OD)  $\delta$  : 1.90-2.08 (1H, m), 2.10-2.30 (5H, m), 2.35-2.55 (1H, m), 2.60-2.78 (2H, m), 3.08 (2H, t, J=10.0Hz), 3.23-3.38 (1H, m), 3.47 (1H, t,

J=10.0 Hz), 3.60-3.83 (5H, m), 4.02-4.11 (1H, m), 4.99-5.08 (1H, m), 5.10-5.18 (1H, m), 6.72-7.04 (4H, m), 7.15-7.24 (2H, m), 7.36-7.44 (6H, m)  
[Example 23]

(R)-5,11-Dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo-  
5 [b,e][1,4]oxazepine dihydrochloride:

(S)-3-Hydroxy-1-(4-pyrrolidinophenethyl)pyrrolidine:

3-Pyrrolidinophenethyl mesylate (1.80 g, 4.00 mmol) synthesized  
in Example 21, (S)-3-pyrrolidinol hydrochloride (0.50 g, 4.05 mmol) and  
potassium carbonate (1.70 g, 12.3 mmol) were added to acetonitrile (20  
10 ml), and they were heated at 100°C for 12 hours. Acetonitrile was  
evaporated under reduced pressure, and the residue was distributed into  
water and ethyl acetate. The intended product was extracted from the  
ethyl acetate layer with 1 M hydrochloric acid. The extract was  
neutralized and then the product was extracted with ethyl acetate. The  
15 organic layer was dried and the solvent was evaporated under reduced  
pressure to obtain (S)-3-hydroxy-1-(3-pyrrolidinophenethyl)pyrrolidine in  
the form of a light yellow solid (1.04 g, 100 %).

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.68-1.80 (1H, m), 1.91-2.02 (4H, m), 2.13-2.25 (1H, m),  
2.30-2.40 (1H, m), 2.55-2.63 (1H, m), 2.67-2.80 (5H, m), 2.89-2.98 (1H, m),  
20 3.15-3.25 (4H, m), 4.28-4.39 (1H, m), 6.39-6.42 (2H, m), 6.50 (1H, d,  
J=8.0 Hz), 7.13 (1H, t, J=8.0 Hz)

(S)-3-Methanesulfonyloxy-1-(3-pyrrolidinophenethyl)pyrrolidine:

(S)-3-Hydroxy-1-(3-pyrrolidinophenethyl)pyrrolidine (1.04 g, 4.00  
mmol) was dissolved in dichloromethane (10 ml). Triethylamine (0.76 ml,  
25 5.49 mmol) and methanesulfonyl chloride (0.39 ml, 5.03 mmol) were  
added to the obtained solution at 0°C and they were stirred overnight.

The reaction mixture was distributed into 5 % aqueous sodium hydrogencarbonate solution and dichloromethane. The organic layer was dried and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the  
5 elution with chloroform and methanol (95:5), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (S)-3-methanesulfonyloxy-1-(3-pyrrolidinophenethyl)pyrrolidine in the form of a light yellow oily substance (1.30 g, 96 %).

E S I / M a s s : 3 3 9 [M + H<sup>+</sup>]

10 N M R (C D C l 3 )  $\delta$  : 1.96-2.02 (4H, m), 2.03-2.15 (1H, m), 2.25-2.38 (1H, m), 2.44-2.54 (1H, m), 2.70-2.80 (4H, m), 2.80-3.02 (3H, m), 3.02 (3H, s), 3.23-3.30 (4H, m), 5.20-5.28 (1H, m), 6.42 (2H, m), 6.50 (1H, d, J=7.5Hz), 7.14 (1H, t, J=7.5Hz)

(R)-5,11-Dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo-  
15 [b,e][1,4]oxazepine dihydrochloride:

60 % sodium hydride (132 mg, 3.3 mmol) was washed with hexane in argon stream and then suspended in dimethyl sulfoxide (10 ml), and the obtained suspension was stirred at room temperature for 30 minutes. 5,11-Dihydrodibenzo[b,e][1,4]oxazepine (600 mg, 3.0 mmol) was added to  
20 the suspension, and they were stirred at room temperature for 30 minutes and then at 50°C for additional 30 minutes. A solution of (S)-3-methanesulfonyloxy-1-(4-pyrrolidinophenethyl)pyrrolidine (340 mg, 1.0 mmol) in dimethyl sulfoxide (5 ml) was added dropwise to the obtained solution, and they were stirred at 50°C for 42 hours. The reaction  
25 mixture was distributed into saturated aqueous sodium chloride solution and ethyl acetate. The organic layer was dried and the solvent was

evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (3:1), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain (R)-5,11-dihydro-5-[1-(3-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo[b,e][1,4]oxazepine in the form of a light yellow oily substance (225 mg, 51 %).

E S I / M a s s : 4 4 0 [M + H<sup>+</sup>]

N M R (C D C l 3 )  $\delta$  : 1.74-1.84 (1H, m), 1.95-2.00 (4H, m), 2.23-2.34 (1H, m), 2.34-2.43 (1H, m), 2.49-2.57 (1H, m), 2.61-2.76 (5H, m), 2.81-2.88 (1H, m), 3.23-3.29 (4H, m), 4.67-4.76 (1H, m), 5.30-5.50 (2H, bs), 6.34-6.48 (3H, m), 6.71-6.85 (3H, m), 6.94-6.97 (1H, m), 7.04-7.16 (3H, m), 7.25-7.32 (2H, m)

The obtained product was treated with 2 M hydrogen chloride / diethyl ether in the same manner as that in Example 21 to obtain the title compound in the form of a brown solid (78 %).

E S I / M a s s : 4 4 0 [M + H<sup>+</sup>]

N M R (C D 3 O D )  $\delta$  : 1.90-2.08 (1H, m), 2.10-2.30 (5H, m), 2.35-2.55 (1H, m), 2.60-2.78 (1H, m), 3.10 (2H, t, J=10.0Hz), 3.25-3.40 (1H, m), 3.25 (2H, t, J=10.0Hz), 3.60-3.80 (5H, m), 4.03-4.12 (1H, m), 4.99-5.09 (1H, m), 5.11-5.19 (1H, m), 6.70-7.04 (5H, m), 7.14-7.47 (7H, m)

[Example 24]

5,11-Dihydro-5-[2-[N-methyl-N-(3-pyrrolidinophenethyl)amino]ethyl]-dibenzo[b,e][1,4]oxazepine dihydrochloride:

5,11-Dihydro-5-[2-(N-methylamino)ethyl]dibenzo[b,e][1,4]-

oxazepine (254 mg, 1.00 mmol, prepared by a method disclosed in International Patent No. 0040570A1), 3-pyrrolidinophenethyl mesylate (296 mg, 1.10 mmol), sodium carbonate (138 mg, 1.30 mmol) and sodium

iodide (20 mg, 0.13 mmol) were added to acetonitrile (20 ml), and they were heated at 90°C under reflux for 6.5 hours. The solvent was evaporated under reduced pressure, and the residue was distributed into ethyl acetate and saturated aqueous sodium hydrogencarbonate solution.

- 5 The organic layer was washed with water and then dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was subjected to the silica gel column chromatography. After the elution with hexane and ethyl acetate (10:1) and then with hexane and ethyl acetate (3:1) as the eluent, suitable fractions were  
10 collected and the solvent was evaporated under reduced pressure to obtain 5,11-dihydro-5-[2-[N-methyl-N-(3-pyrrolidinophenethyl)amino]-ethyl]dibenzo[b,e][1,4]oxazepine in the form of a light yellow oily substance (331 mg, 78 %).

E S I / M a s s : 4 2 8 [M+H<sup>+</sup>]

- 15 NMR (CDCl<sub>3</sub>) δ : 1.96-2.00(4H, m), 2.32(3H, s), 2.61(4H, s), 2.66(2H, t, J=8.0Hz), 3.23-3.27(4H, m), 3.90(2H, t, J=8.0Hz), 5.29(2H, s), 6.32-6.44(3H, m), 6.77-6.84(3H, m), 7.00-7.14(4H, m), 7.25-7.32(2H, m)

- The obtained product was treated with 2 M hydrogen chloride / diethyl ether in the same manner as that in Example 21 to obtain the title  
20 compound in the form of a brown solid (81 %).

E S I / M a s s : 4 2 8 [M+H<sup>+</sup>]

- NMR (CDCl<sub>3</sub>) δ : 2.28-2.40(4H, m), 2.85(3H, d, J=4.3Hz), 3.10-3.48(6H, m), 3.55-3.74(4H, m), 4.23-4.35(1H, m), 4.40-4.52(1H, m), 5.23(1H, d, J=14.3Hz), 5.25(1H, d, J=14.3Hz), 6.82-6.93(3H, m), 7.06-7.11(2H, m),  
25 7.18(1H, d, J=8.7Hz), 7.24-7.44(4H, m), 7.53(1H, d, J=8.7Hz), 7.78(1H,

m)

[Example 25]

(R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine dihydrochloride (= compound of

5 Example 8):

Methyl ester of N-[(4-dimethylaminophenyl)acetyl]-D-proline:

1-Hydroxybenzotriazole monohydrate (6.1 g, 45.4 mmol) and N-dimethylaminopropyl-N'-ethylcarbodiimide hydrochloride (8.7 g, 45.4 mmol) were added to a solution of (4-dimethylaminophenyl)acetic acid (7.4 g, 41.3 mmol) and methyl ester hydrochloride of D-proline (7.19 g, 43.4 mmol) in methylene chloride (150 ml). The obtained mixture was stirred at room temperature for 6 hours. Triethylamine (6.3 ml, 45.4 mmol) was added to the mixture. They were stirred at room temperature overnight and the reaction mixture was successively washed with water (200 ml), 5 % aqueous sodium hydrogencarbonate solution (200 ml) and water (200 ml). The solvent was evaporated under reduced pressure. The obtained residue was subjected to the silica gel column chromatography. After the elution with methylene chloride and methanol (10:1), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain the title compound in the form of a brown oily substance (11.0 g, 83 %).

ESI / Mass : 291 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.82-2.26 (4H, m), 2.82-2.98 (6H, m), 3.40-3.76 (2H, m), 3.60 (3H, s), 3.73 (2H, s), 4.41-4.52 (1H, m), 6.64-6.74 (2H, m), 7.07-7.19 (2H, m)

N-[(4-dimethylaminophenyl)acetyl]-D-proline:



Methyl ester of N-[(4-dimethylaminophenyl)acetyl]-D-proline (1.0 g, 3.4 mmol) was dissolved in tetrahydrofuran (10 ml). Water (10 ml) and 1 M aqueous sodium hydroxide solution (3.7 ml, 3.7 mmol) were added to the obtained solution. They were stirred at room temperature overnight. A saturated aqueous ammonium chloride solution (15 ml) was added to the reaction mixture, and they were adjusted to around pH 4 with 1 M hydrochloric acid. After the solvent was evaporated from the mixture under reduced pressure, acetone was added to the residue and they were stirred. The reaction mixture was filtered to obtain the filtrate. The solvent was evaporated under reduced pressure and the residue was dried to obtain the title compound in the form of a yellow solid (0.91 g, 96 %).

E S I / M a s s : 2 7 7 [M + H<sup>+</sup>]

N M R (CDCl<sub>3</sub>) δ : 1.80-2.28 (3H, m), 2.45-2.58 (1H, m), 2.95 (6H, s), 3.42-3.70 (2H, m), 3.65 (2H, s), 4.60-4.68 (1H, m), 6.72-6.83 (2H, m), 7.08-7.19 (2H, m)

(R)-1-[(4-dimethylaminophenyl)acetyl]pyrrolidine-2-carboxylic acid [2-(2-bromo-4-chlorobenzyloxy)phenyl]amide:

Toluene (111 ml) and N-methylmorpholine (3.85 ml, 35.0 mmol) were added to N-[(4-dimethylaminophenyl)acetyl]-D-proline (8.56 g, 31.0 mmol). Ethyl chloroformate (3.26 ml, 34.1 mmol) was added to the obtained mixture, and they were stirred for 2 hours. 2-(2-Bromo-4-chlorobenzyloxy)aniline hydrochloride (10.8 g, 31.0 mmol) and N-methylmorpholine (4.09 ml, 37.2 mmol) were added thereto and they were stirred at room temperature overnight. Water (40 ml) was added to the reaction mixture. The organic layer was washed with water (40 ml) and

then dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with methylene chloride and methanol (30:1), suitable fractions were collected and the solvent was  
5 evaporated under reduced pressure to obtain the title compound in the form of a yellow solid (16.3 g, 92 %).

E S I / M a s s : 5 7 2 [M+H<sup>+</sup>]

N M R (CDCl<sub>3</sub>) δ : 1.80-1.94(1.2H, m), 1.96-2.06(0.8H, m), 2.08-2.36(1.2H, m), 2.51-2.59(0.8H, m), 2.79 and 2.92(total 6.0H, each s),  
10 3.45-3.75(4H, m), 4.53-4.59(0.2H, m), 4.81-4.87(0.8H, m), 4.94-5.13(0.3H, m), 5.13(1.7H, s), 6.47-6.69(2.0H, m), 6.84-7.14(5.1H, m), 7.19-7.26(0.9H, m), 7.51-7.68(1.9H, m), 8.26(0.1H, br s), 8.35-8.42(1.0H, m), 9.53(1H, br s)

(R)-{[2-(3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine-5-carbonyl)-pyrrolidine]-1-yl}-2-(4-dimethylaminophenyl)ethanone:  
15

Potassium carbonate (1.27 g, 9.19 mmol), copper bromide (I) (24.1 mg, 0.168 mmol) and 4-picoline (8.65 ml) were added to (R)-1-[(4-dimethylaminophenyl)acetyl]pyrrolidine-2-carboxylic acid [2-(2-bromo-4-chlorobenzoyloxy)phenyl]amide (1.73 g, 3.03 mmol). They were heated at  
20 145°C for 20 hours and then filtered. The solvent was evaporated from the filtrate under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with methylene chloride and methanol (20:1), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain the title  
25 compound in the form of a brown solid (0.97 g, 66 %).

E S I / M a s s : 4 9 0 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.52-2.34 (4H, m), 2.92 and 2.96 (total 6.0H, each s),  
3.44-3.77 (4.1H, m), 4.34-4.41 (0.2H, m), 4.65-4.72 (0.4H, m), 4.77-  
4.91 (1.1H, m), 5.08-5.15 (0.2H, m), 5.50-5.67 (0.3H, m), 6.34-6.41 (0.7H,  
m), 6.65-7.03 (4.0H, m), 7.06-7.50 (6.5H, m), 7.59 (0.2H, br s), 7.91-  
5 7.96 (0.2H, m), 8.11 (0.1H, br s)

(R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine:

(R)-{[2-(3-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine-5-carbonyl)-pyrrolidine]-1-yl}-2-(4-dimethylaminophenyl)ethanone (0.97 g,  
10 1.98 mmol) was dissolved in tetrahydrofuran (19.4 ml). Sodium borohydride (0.39 g, 10.4 mmol) was added to the resultant solution. Then boron trifluoride / tetrahydrofuran complex (1.69 ml, 13.9 mmol) was added to the obtained mixture in an ice bath. The reaction mixture was heated at 37°C for 42 hours. Sodium borohydride (0.056 g, 1.5  
15 mmol) and boron trifluoride / tetrahydrofuran complex (0.24 ml, 1.99 mmol) were added thereto. The reaction mixture was heated at 37°C for 24 hours. 1.5 M aqueous sodium hydroxide solution (16 ml, 24 mmol) was added thereto under cooling in the ice bath. The reaction mixture was heated at 60°C for 12 hours and then distributed into toluene (20 ml)  
20 and water (10 ml). The organic layer was taken. Tetrahydrofuran was evaporated under reduced pressure. The residue was washed with water (10 ml) and then the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with methylene chloride and methanol (10:1), suitable  
25 fractions were collected and the solvent was evaporated under reduced pressure to obtain the title compound in the form of a brown solid (0.67 g,

74 %).

E S I / M a s s : 4 6 2 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.59-1.90 (4H, m), 2.22-2.31 (1H, m), 2.50-2.59 (1H, m),  
2.66-2.84 (3H, m), 2.93 (6H, s), 2.97-3.06 (1H, m), 3.16-3.24 (1H, m),  
5 3.34 (1H, dd, J=13.0, 9.4Hz), 4.07 (1H, dd, J=13.0, 3.7Hz), 5.22 (2H, s),  
6.70-6.75 (2H, m), 6.75-6.86 (3H, m), 6.97-7.02 (2H, m), 7.08-7.14 (3H, m),  
7.17 (1H, d, J=7.9Hz)

(R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

10 (R)-3-Chloro-5,11-dihydro-5-[1-(4-dimethylaminophenethyl)-pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine (10.6 g, 22.9 mmol) was dissolved in 2-propanol (100 ml). 4 M hydrogen chloride / 2-propanol (22.9 ml) was added to the obtained solution. The solvent was evaporated under reduced pressure, and 4 M hydrogen chloride / 2-propanol (11.5 ml) was added to the residue. The solvent was evaporated  
15 under reduced pressure to obtain the title compound in the form of a light yellow solid (12.9 g, 100 %).

E S I / M a s s : 4 6 2 [M+H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 2.00-2.21 (2H, m), 2.21-2.34 (2H, m), 2.86-2.98 (1H, m),  
20 3.03-3.15 (1H, m), 3.19 (6H, s), 3.15-3.30 (1H, m), 3.47-3.70 (3H, m),  
3.90-4.00 (1H, m), 4.24 (1H, dd, J=14.0, 7.2Hz), 4.65 (1H, dd, J=14.0, 6.0Hz), 5.12 (1H, d, J=12.7Hz), 5.40 (1H, d, 12.7Hz), 6.87 (1H, dd, J=7.8, 1.9Hz), 6.89-7.00 (2H, m), 7.03-7.09 (2H, m), 7.14 (1H, d, J=1.9Hz), 7.18 (1H, d, J=8.0Hz), 7.45 (2H, d, J=8.4Hz), 7.79 (2H, d, J=8.6Hz)

25

[Example 26]

(R)-2-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride (= compound of Example 9):

5 (4-Pyrrolidinophenyl)acetic acid:

Toluene (10 ml) was added to a mixture of palladium acetate (22.3 mg, 0.10 mmol), 2-(biphenyl)-di-tert-butylphosphine (59.8 mg, 0.20 mmol) and sodium tert-butoxide (2.40 g, 25.0 mmol), and then (4-bromophenyl)acetic acid (2.15 g, 10.0 mmol) and pyrrolidine (1.10 ml, 10 13.2 mmol) were added thereto. The obtained mixture was heated at 70°C for 46 hours. Water (20 ml) was added to the reaction mixture. pH of the aqueous layer was controlled at 2 or below. The aqueous layer was washed with toluene and adjusted to pH 4 to 5. After stirring the reaction mixture in ice-bath for a while, it was filtered to obtain the title 15 compound in the form of a light yellow solid (1.1 g, 54 %).

E S I / M a s s : 2 0 6 [M+H<sup>+</sup>]

N M R (DMSO-d<sub>6</sub>) δ : 1.90-1.95 (4H, m), 3.15-3.20 (4H, m), 3.38 (2H, s), 6.47 (2H, d, J=8.4Hz), 7.03 (2H, d, J=8.4Hz)

Methyl ester of N-[(4-pyrrolidinophenyl)acetyl]-D-proline:

20 Methylene chloride (20 ml) was added to a mixture of (4-pyrrolidinophenyl) acetic acid (2.05 g, 10.0 mmol) and methyl ester hydrochloride of D-proline (1.66 g, 10.0 mmol). Triethylamine (1.55 ml, 11.1 mmol) and N-dimethylaminopropyl-N'-ethylcarbodiimide hydrochloride (2.11 g, 11.0 mmol) were added thereto. The obtained 25 mixture was stirred at room temperature for 4 hours. Then the reaction mixture was successively washed with water (10 ml), water (5 ml), 5 %

aqueous citric acid solution (5 ml) and 5 % aqueous sodium hydrogencarbonate solution (5 ml). After drying over magnesium sulfate, the solvent was evaporated under reduced pressure to obtain the title compound in the form of a light red solid (3.06 g, 96 %).

5 NMR ( $\text{CDCl}_3$ )  $\delta$  : 1.85-2.15 (8H, m), 3.23-3.28 (4H, m), 3.31-3.68 (4H, m), 3.68-3.75 (3H, m), 4.40-4.53 (1H, m), 6.45-6.54 (2H, m), 7.05-7.14 (2H, m)  
N-[(4-Pyrrolidinophenyl)acetyl]-D-proline:

Methyl ester of N-[(4-pyrrolidinophenyl)acetyl]-D-proline (30.1 g, 94.2 mmol) was dissolved in tetrahydrofuran (150 ml). Water (134 ml)  
10 and 6 M aqueous sodium hydroxide solution (16.5 ml, 99.2 mmol) were added to the obtained solution. They were stirred at room temperature for 4 hours. 6 M Hydrochloric acid (16.6 ml, 99.7 mmol) was added to the reaction mixture. Tetrahydrofuran was evaporated from the mixture under reduced pressure and then the residue was left to stand in a  
15 refrigerator overnight and then filtered. After drying the filter cake under reduced pressure, the title compound was obtained in the form of a light purple solid (23.4 g, 82 %).

E S I / M a s s : 3 0 3  $[\text{M} + \text{H}^+]$

NMR ( $\text{CDCl}_3$ )  $\delta$  : 1.85-2.05 (7H, m), 2.45-2.55 (1H, m), 3.23-3.29 (4H, m),  
20 3.45-3.70 (4H, m), 4.60-4.64 (1H, m), 6.48-6.55 (2H, m), 7.07-7.11 (2H, m)  
(R)-1-[(4-Pyrrolidinophenyl)acetyl]pyrrolidine-2-carboxylic acid [2-(2-bromo-5-fluorobenzyloxy)phenyl]amide:

Toluene (37.8 ml) and N-methylmorpholine (1.10 g, 10.8 mmol) were added to N-[(4-pyrrolidinophenyl)acetyl]-D-proline (2.90 g, 9.59  
25 mmol). Ethyl chloroformate (1.14 g, 10.5 mmol) was added to the obtained mixture in an ice bath, and they were stirred for 2 hours. 2-

(2-Bromo-5-fluorobenzyloxy)aniline hydrochloride (3.19 g, 9.59 mmol) and N-methylmorpholine (1.16 g, 11.5 mmol) were added thereto and the temperature of the obtained mixture was slowly elevated to room temperature for a period of 16 hours. Water (30 ml), citric acid (1.61 g) and toluene (10 ml) were added to the reaction mixture for the distribution. The organic layer was washed with water (10 ml), water (10 ml), 6.7 % aqueous sodium hydrogencarbonate solution (10 ml), 6.7 % aqueous sodium hydrogencarbonate solution (10 ml), water (10 ml) and water (10 ml). After drying over sodium sulfate, the solvent was evaporated under reduced pressure to obtain the title compound in the form of a light yellow solid (5.13 g, 93 %).

E S I / M a s s : 5 8 0 [M + H<sup>+</sup>]

NMR (CDCl<sub>3</sub>) δ : 1.77-2.20 (7H, m), 2.48-2.57 (1H, m), 3.14-3.25 (4H, m), 3.42-3.67 (4H, m), 4.80-4.88 (1H, m), 5.11 (2H, s), 6.29-6.46 (2H, m), 6.80-7.10 (6H, m), 7.43-7.61 (2H, m), 8.26-8.39 (1H, m), 9.57 (1H, s) (R)-{[2-(2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine-5-carbonyl)-pyrrolidine]-1-yl}-2-(4-pyrrolidinophenyl)ethanone:

Potassium carbonate (3.58 g, 25.9 mmol), copper bromide (I) (63.5 mg, 0.443 mmol) and 4-picoline (25 ml) were added to (R)-1-[(4-pyrrolidinophenyl)acetyl]pyrrolidine-2-carboxylic acid [2-(2-bromo-5-fluorobenzyloxy)phenyl]amide (5.0 g, 8.61 mmol). They were heated at 145°C for 21 hours and then filtered to obtain the filtrate. The solvent was evaporated from the filtrate under reduced pressure. The obtained mixture was distributed into toluene and 9.5 % aqueous citric acid solution. The organic layer was washed with 9.5 % aqueous citric acid solution twice and then dried over sodium sulfate. The solvent was

evaporated under reduced pressure. The residue was subjected to the silica gel column chromatography. After the elution with methylene chloride and methanol (97:3), suitable fractions were collected and the solvent was evaporated under reduced pressure to obtain the title  
5 compound in the form of a purple solid (4.16 g, 97 %).

E S I / M a s s : 5 0 0 [M+H<sup>+</sup>]

N M R (CDCl<sub>3</sub>) δ : 1.60-2.40 (8H, m), 3.14-3.35 (4H, m), 3.39-3.75 (4H, m),  
4.29-5.68 (3H, m), 6.32-6.60 (3H, m), 6.77-8.11 (8H, m)

(R)-2-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-  
10 methyl]dibenzo[b,e][1,4]oxazepine:

(R)-{[2-(2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine-5-carbonyl)pyrrolidine]-1-yl}-2-(4-pyrrolidinophenyl)ethanone (3.79 g, 7.59 mmol) was dissolved in tetrahydrofuran (48 ml). Sodium borohydride (1.52 g, 40.2 mmol) was added to the resultant solution. Then boron  
15 trifluoride / tetrahydrofuran complex (7.38 g, 49.5 mmol) was added to the obtained mixture in an ice bath. The reaction mixture was heated at 37°C for 66 hours. 1.5 M aqueous sodium hydroxide solution (48 ml, 75 mmol) was added thereto under cooling in the ice bath. The reaction mixture was heated at 60°C for 13 hours and then toluene (12 ml) was  
20 added thereto. The organic layer was taken. The solvent was evaporated under reduced pressure to obtain 21.0 g of the residue. Toluene (12 ml) was added thereto. The obtained mixture was washed with water (10 ml) twice, and the solvent was evaporated under reduced pressure. The residue was subjected to the silica gel column  
25 chromatography. After the elution with methylene chloride and methanol (97:3), suitable fractions were collected and the solvent was



evaporated under reduced pressure to obtain the title compound in the form of a purple solid (2.95 g, 82 %).

E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

N M R (C D C l <sub>3</sub>) δ : 1.59-1.90 (4H, m), 1.90-2.10 (4H, m), 2.18-2.30 (1H, m),  
5 2.42-2.58 (1H, m), 2.62-2.83 (3H, m), 2.92-3.08 (1H, m), 3.12-3.38 (6H, m),  
4.08 (1H, dd, J=12.8, 3.0Hz), 5.16 (1H, d, J=11.8Hz), 5.30 (1H, d, J=11.8Hz), 6.54 (2H, d, J=8.5Hz), 6.72-6.86 (3H, m), 6.93-7.12 (6H, m)  
(R)-2-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-yl-methyl]dibenzo[b,e][1,4]oxazepine dihydrochloride:

10 (R)-2-Fluoro-5,11-dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-2-ylmethyl]dibenzo[b,e][1,4]oxazepine (12.04 g, 25.5 mmol) was dissolved in 2-propanol (250 ml). 4 M hydrogen chloride / 2-propanol (17.0 ml) was added to the obtained solution and they were stirred at room temperature for 0.5 hour. The solvent was evaporated under reduced pressure, and  
15 2-propanol (about 50 ml) was added to the residue. The solvent was evaporated under reduced pressure repeatedly 4 times to obtain the title compound in the form of a light red solid (14.89 g, 100 %).

E S I / M a s s : 4 7 2 [M + H<sup>+</sup>]

N M R (D M S O - d <sub>6</sub>) δ : 1.76-2.19 (8H, m), 2.89-3.25 (4H, m), 3.33-3.54 (5H,  
20 m), 3.54-3.67 (2H, m), 4.10 (1H, dd, J=13.6, 7.5Hz), 4.39 (1H, dd, J=13.6, 6.5Hz), 5.18 (1H, d, J=12.0Hz), 5.44 (1H, d, J=12.1Hz), 6.72-6.78 (1H, m), 6.83-6.90 (2H, m), 6.96-7.27 (6H, m), 7.31-7.38 (2H, m)

[Example 27]

(R)-5,11-Dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo-  
25 [b,e][1,4]oxazepine (= compound of Example 22):

(R)-N-[1-(4-Pyrrolidinophenethyl)pyrrolidin-3-yl]-2-(2-bromobenzyloxy)-

aniline:

(S)-3-Methanesulfonyloxy-1-(4-pyrrolidinophenethyl)pyrrolidine (0.30 g, 0.89 mmol) was added to 2-(2-bromobenzyloxy)aniline (1.15 g, 4.13 mmol) in argon stream. The obtained mixture was dissolved in acetonitrile (50 ml). Potassium carbonate (1.62 g, 11.7 mmol) was added to the obtained solution, and they were refluxed for 85 hours. Acetonitrile (15 ml) was added to the reaction mixture, and they were refluxed for additional 48 hours. The reaction mixture was filtered through Celite to obtain the filtrate. The solvent was evaporated under reduced pressure to obtain the title compound in the form of a brown oily mixture (1.40 g).

ESI / Mass : 520 [M+H<sup>+</sup>]

(R)-5,11-Dihydro-5-[1-(4-pyrrolidinophenethyl)pyrrolidin-3-yl]dibenzo-[b,e][1,4]oxazepine:

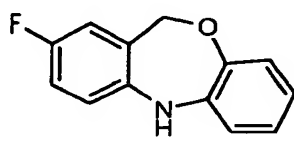
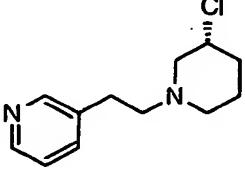
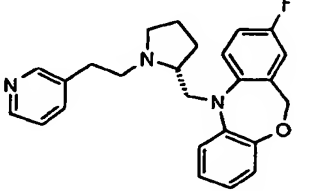
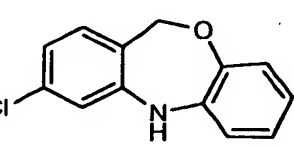
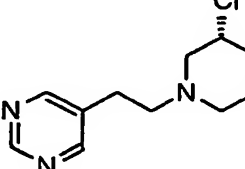
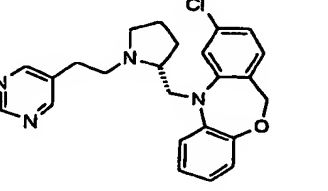
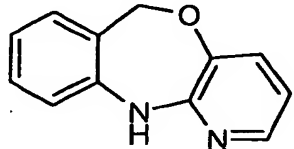
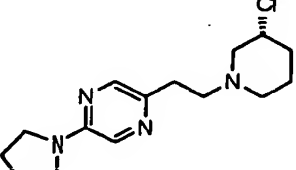
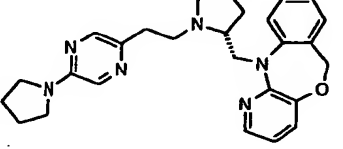
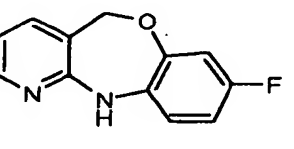
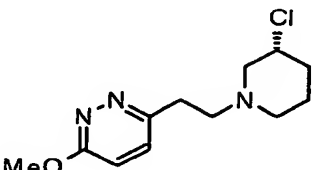
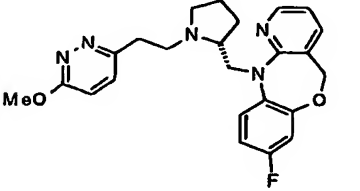
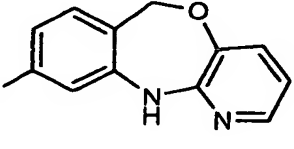
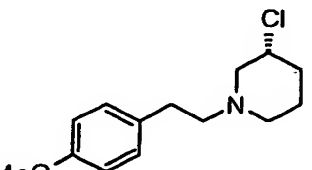
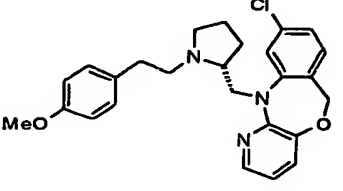
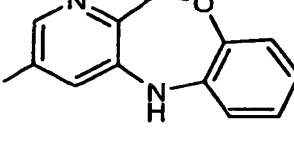
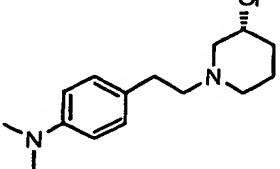
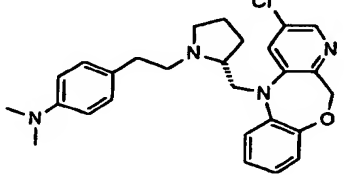
Potassium carbonate (1.71 g, 12.4 mmol), copper bromide (I) (53 mg, 0.37 mmol) and toluene (30 ml) were added to (R)-N-[1-(4-pyrrolidinophenethyl)pyrrolidin-3-yl]-2-(2-bromobenzyloxy)aniline (1.4 g as mixture). The reaction mixture was heated under reflux for 53 hours and then copper bromide (I) (60 mg, 0.42 mmol) was added thereto. The reaction mixture was heated under reflux for additional 50 hours. Toluene (10 ml), potassium carbonate (1.04 g, 7.52 mmol) and copper bromide (I) (42 mg, 0.29 mmol) were added thereto. The reaction mixture was heated under reflux for 48 hours and then filtered through Celite. Water was added to the filtrate. The organic layer was taken and dried over sodium sulfate. The solvent was evaporated under reduced pressure. A part (187 mg) of the obtained residue (1.12 g) was

subjected to the high performance liquid chromatography. After the elution with acetonitrile and water (gradient from 20:80 to 70:30), suitable fractions were collected and distributed into methylene chloride and saturated aqueous sodium hydrogencarbonate solution. The organic  
5 layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to the thin layer silica gel chromatography. After the development with hexane and ethyl acetate (1:5), silica gel was collected from proper parts and then eluted with a solvent mixture of methylene chloride and methanol (3:1). The  
10 effluents were collected, and the solvent was evaporated under reduced pressure to obtain the title compound in the form of a white solid (25.5 mg, yield in 2 steps: 39 %).

E S I / M a s s : 4 4 0 [M+H<sup>+</sup>]

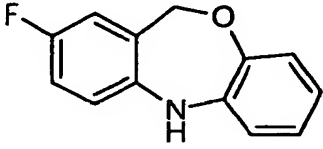
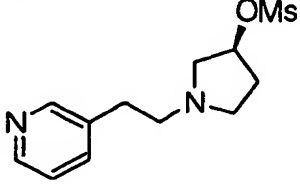
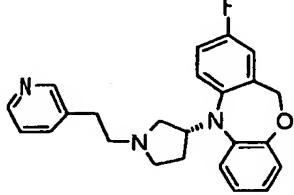
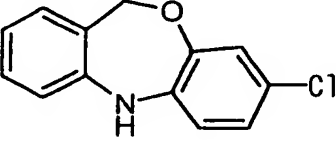
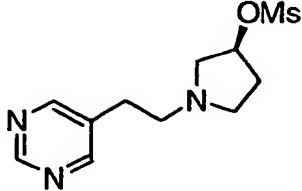
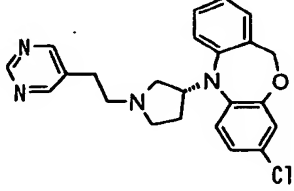
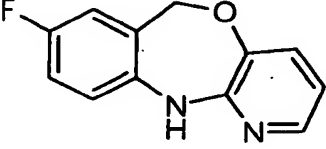
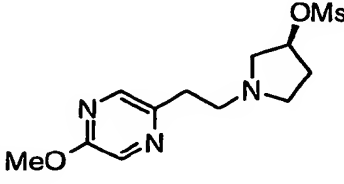
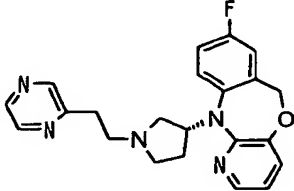
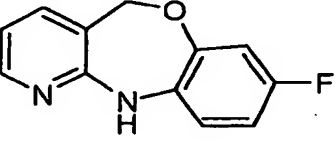
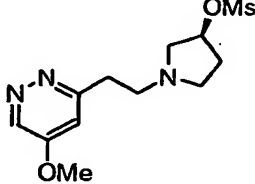
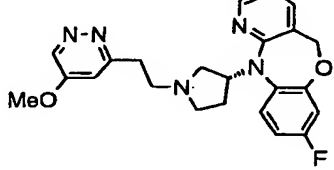
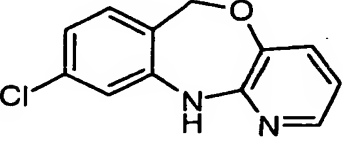
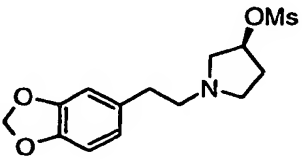
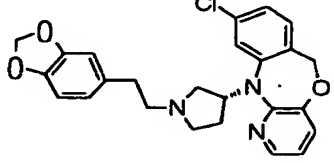
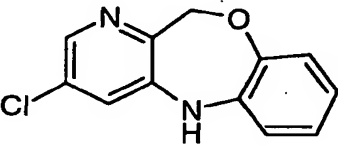
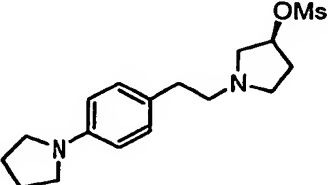
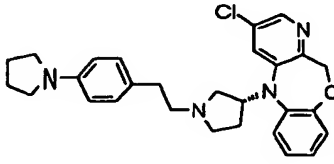
N M R (CDCl<sub>3</sub>) δ : 1.72-1.84(1H, m), 1.92-2.05(4H, m), 2.24-2.49(2H, m),  
15 2.49-2.77(5H, m), 2.82-2.94(1H, m), 3.18-3.36(5H, m), 4.68-4.79(1H, m),  
5.19-5.62(2H, m), 6.48(2H, d, J=8.4Hz), 6.70-6.85(3H, m), 6.95(1H, dd, J=7.8, 1.6Hz), 7.02(2H, d, J=8.6Hz), 7.03-7.14(2H, m), 7.25-7.35(2H, m)  
[Example 28]

Compounds [II] shown in Table 1 can be produced in the same  
20 manner as that in Example 1 except that 3-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was replaced with a compound [V] shown in Table 1 and that (R)-3-chloro-1-(4-methoxyphenethyl)piperidine was replaced with a compound [VI] shown in Table 1.

Table 1		
raw material [V]	raw material [VI]	product [II]
		
		
		
		
		
		

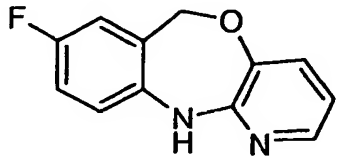
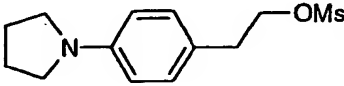
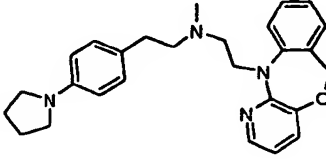
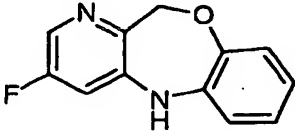
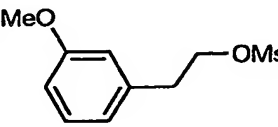
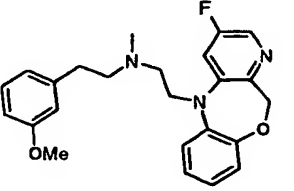
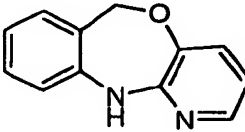
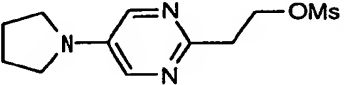
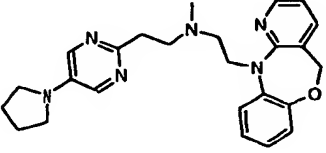
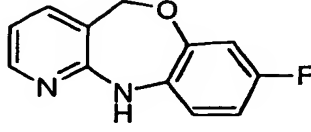
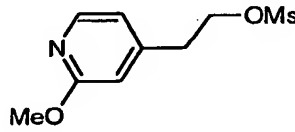
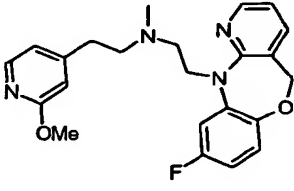
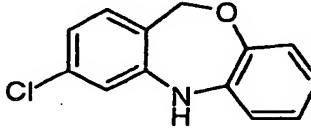
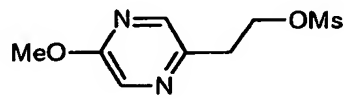
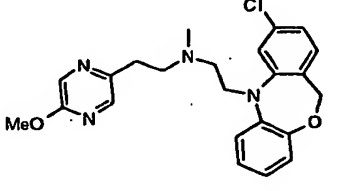
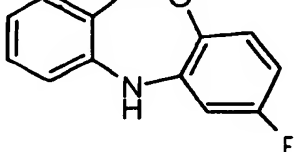
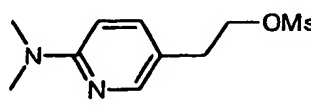
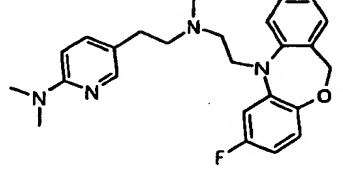
[Example 29]

Compounds [III] shown in Table 2 can be produced in the same manner as that in Example 16 except that 2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was replaced with a compound [V] shown in Table 2 and that (S)-1-(4-dimethylaminophenethyl)-3-methanesulfonyloxypirrolidine was replaced with a compound [XI] shown in Table 2.

Table 2		
raw material [V]	raw material [XI]	product [III]
		
		
		
		
		
		

[Example 30]

Compounds [IV] shown in Table 3 can be produced in the same manner as that in Example 24 except that 2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was replaced with a compound [V]  
5 shown in Table 3 and that 3-pyrrolidinophenethyl mesylate was replaced with a compound [X] shown in Table 3.

Table 3		
raw material [V]	raw material [X]	product [IV]
		
		
		
		
		
		



<Preparation Examples>

Preparation Examples will be given below.

[Preparation Example 1]

The following ingredients were mixed together by an ordinary method and then tableted to obtain a tablet containing 50 mg of the active ingredient.

	Compound of Example 8	50 mg
	Lactose	200 mg
	Crystalline cellulose	40 mg
10	Magnesium stearate	5 mg

[Preparation Example 2]

A mixture of the following ingredients was granulated by an ordinary method to obtain granules.

	Compound of Example 8	50 mg
15	Lactose	90 mg
	Corn starch	60 mg
	Talc	30 mg
	Magnesium stearate	10 mg

<Test Examples>

The description will be made below on the pharmacological tests of the compounds of the present invention.

[Test Example 1] *In vitro* calcium channel antagonism (blood vessel):

The thoracic aorta of each male Crj:CD rat (8 to 12 weeks old) was extracted to form a spiral preparation. The blood vessel preparation was suspended in a Tyrode's solution of 37°C which was oxygenated with a mixed gas (containing 95 % oxygen and 5 % carbon

dioxide). The change in the tension of the blood vessel was isometrically recorded on a pen-writing recorder through a transducer. The high potassium-induced contraction was caused by replacing a normal Tyrode's solution with a high potassium Tyrode's solution (containing 94.6 mM of NaCl, 45.0 mM of KCl, 1.8 mM of  $\text{CaCl}_2$ , 1.04 mM of  $\text{MgCl}_2$ , 0.4 mM of  $\text{NaH}_2\text{PO}_4$ , 11.9 mM of  $\text{NaHCO}_3$  and 5.55 mM of glucose). The effect of the test compound to inhibit the contraction by high potassium was determined by 30 minutes pretreatment. The calcium channel antagonistic activity is evaluated in terms of the concentration ( $\text{IC}_{50}$ ) of the test compound showing the 50 % inhibition of the contraction (Table 4).

[Test Example 2] *In vitro* calcium channel antagonism (ileum):

The ileum was extracted from a portion which was 3 cm apart from the ileocecal region of each male Crj:CD rat (8 to 12 weeks old). The ileum preparation thus obtained was suspended in a Tyrode's solution of 37°C in which was oxygenated with a mixed gas (containing 95 % oxygen and 5 % carbon dioxide). The change in the tension of the ileum was isotonicly recorded on a pen-writing recorder through a transducer. The high potassium-induced contraction was caused by replacing a normal Tyrode's solution with a high potassium Tyrode's solution (containing 94.6 mM of NaCl, 45.0 mM of KCl, 1.8 mM of  $\text{CaCl}_2$ , 1.04 mM of  $\text{MgCl}_2$ , 0.4 mM of  $\text{NaH}_2\text{PO}_4$ , 11.9 mM of  $\text{NaHCO}_3$  and 5.55 mM of glucose). The effect of the test compound to inhibit the contraction by high potassium was determined by 30 minutes pretreatment. The calcium channel antagonistic activity is evaluated in terms of the concentration ( $\text{IC}_{50}$ ) of the test compound showing the 50 % inhibition of

the contraction (Table 4). The ratio of the  $IC_{50}$  for the blood vessel to the  $IC_{50}$  for the ileum is also shown as the selectivity in Table 4.

Table 4

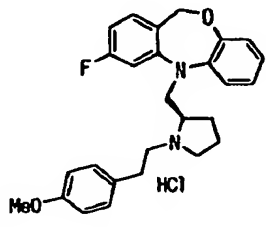
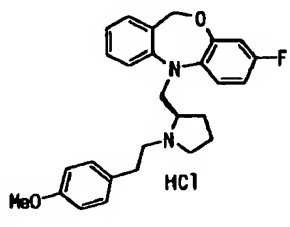
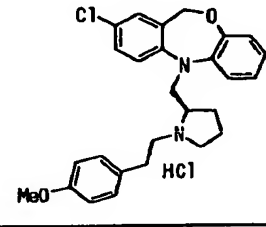
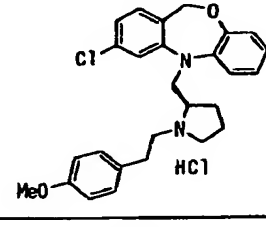
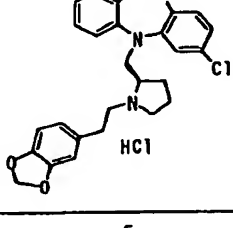
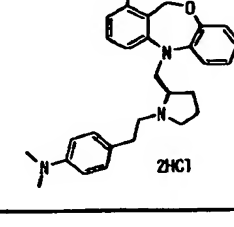
Example No.	structural formula	IC <sub>50</sub> (nM) blood vessel <sup>a)</sup>	IC <sub>50</sub> (nM) ileum <sup>b)</sup>	selectivity a/b
1		163.0	22.0	7.4
2		186.3	19.0	9.8
3		556.7	39.0	14.3
4		107.0	17.5	6.1
5		590.3	71.0	8.3
6		631.0	79.7	7.9

Table 4 (continued)

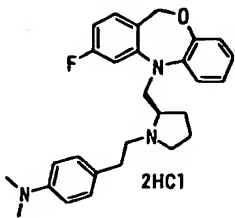
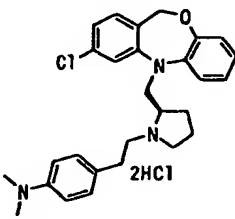
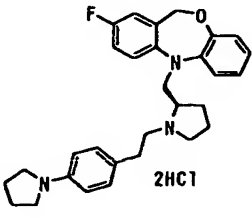
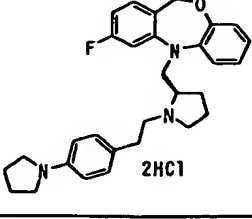
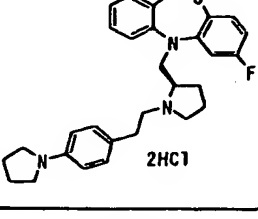
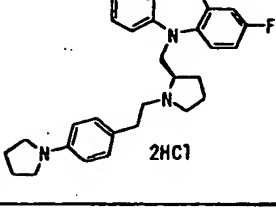
7	 2HCl	121.0	19.8	6.1
8	 2HCl	236.0	6.1	38.7
9	 2HCl	134.7	15.0	9.0
10	 2HCl	142.7	12.6	11.3
11	 2HCl	145.0	11.0	13.2
12	 2HCl	193.3	14.2	13.6

Table 4 (continued)

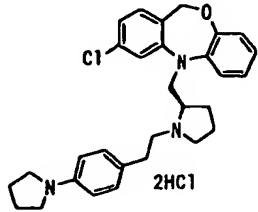
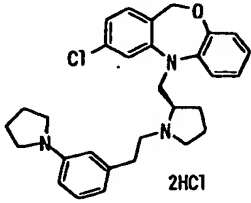
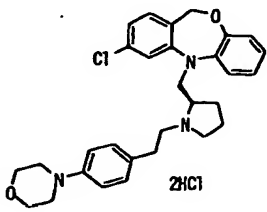
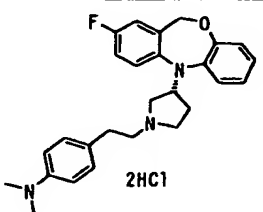
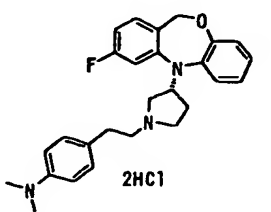
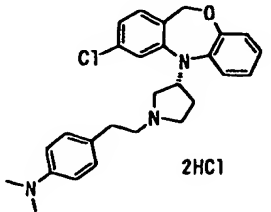
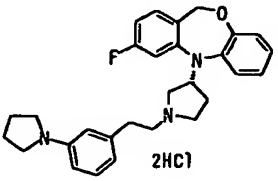
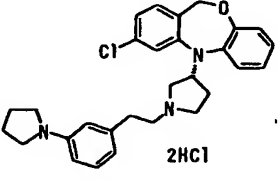
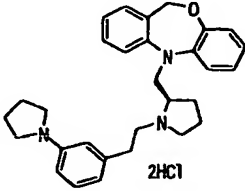
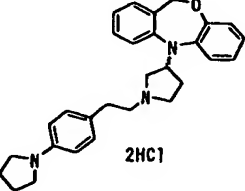
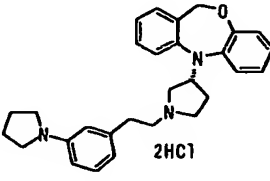
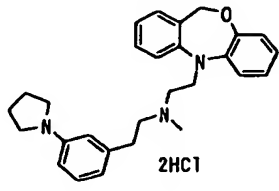
13	 2HCl	156.7	15.3	10.2
14	 2HCl	611.3	82.5	7.4
15	 2HCl	22.7	9.0	2.5
16	 2HCl	92.7	12.0	7.7
17	 2HCl	64.0	8.4	7.6
18	 2HCl	42.3	5.6	7.6

Table 4 (continued)

Example No.	structural formula	IC <sub>50</sub> (nM) blood vessel <sup>a)</sup>	IC <sub>50</sub> (nM) ileum <sup>b)</sup>	selectivity a/b
19	 2HCl	95.3	15.3	6.2
20	 2HCl	67.3	11.1	6.1
21	 2HCl	813.3	59.5	13.7
22	 2HCl	114.3	13.3	8.6
23	 2HCl	158.3	17.3	9.2
24	 2HCl	274.0	33.8	8.1

It was confirmed from the results shown in Table 4 that the compounds of the present invention have an extremely strong calcium channel antagonistic effect and that they are calcium channel antagonists  
5 having a high selectivity toward the intestinal tracts. Although International Patent Nos. 9912925A1 and 0040570A1 disclose the calcium antagonistic effect of various 5,11-dihydroibenzo[b,e][1,4]oxazepine derivatives tested by the same method, it was confirmed that the compounds of the present invention are superior to those compounds in  
10 the antagonistic effect on the intestinal tracts and the selectivity toward the intestinal tracts.

[Test Example 3] Effects on *in vivo* 5-hydroxytryptophan (5-HTP)-induced defecation models of mice:

The tests were conducted by a method of G. J. Sanger et al.  
15 (British Journal of Pharmacology, 130: 706-712, 2000).

Male SLC:ICR mice (6 weeks old) were moved to 5 stainless steel cages connected together for mice. After the naturalization for at least one hour, a test compound was orally administered (n = 10). 30 minutes after, 10 mg / 5 mL / kg of 5-HTP or vehicle ( 5 mL / kg of physiological  
20 saline for a group for which 5-HTP was not used) was injected subcutaneously. The state of the fecal pellets of each mouse excreted in 30 minutes immediately after the injection was observed [scored as 0 (normal fecal pellets or no fecal pellets) or 1 (diarrhea or loose stool)]. The score obtained by subtracting the score of the group to which 5-HTP  
25 had not been given from the score of the group to which 5-HTP had been given was taken as 100 %. The amount of a test compound for 50 %



control (ID50) was calculated.

ID50 in Example 8 was 8.3 mg/kg.

[Test Example 4] Effect of elevating the threshold value of abdominal pain in *in vivo* rat colorectal distension models :

5        The tests were conducted by a method of Saito et al. (Anesth. Analg. 1998; 87: 382-387).

10        Male Crj:CD rats (250-350 g) were used. A test compound was orally administered to them (n = 8). A balloon (length: 7 cm) for dilating the colon was connected to a transducer. After fasting each rat for one day, the balloon was noninvasively inserted internally into the colorectal portion and the base of the balloon was positioned 1 cm from anus under light anesthesia with ether. Water was injected into the balloon at a rate of 0.9 ml/min until the inner pressure in the balloon reached 100 mmHg (cut off value). When the contraction of the abdominal muscle was  
15        macroscopically observed during the colon distension, the pressure in the balloon was taken as the threshold value of abdominal pain. The colon distension was conducted at intervals of at least 5 minutes.

The analgesic effect was determined according to the following formula:

20        
$$\text{Analgesic effect (\%)} = \frac{[(\text{threshold value of abdominal pain after treatment with test compound}) - (\text{threshold value of abdominal pain before treatment with test compound})]}{[100 - (\text{threshold value of abdominal pain before treatment with test compound})]} \times 100.$$

25        The analgesic effect was calculated as the dose of the test compound required for 50 % control (ID50).

ID50 in Example 8 was 2.6 mg/kg and that in Example 12 was 1.9

mg/kg.

It was confirmed that when the test compounds of the present invention were orally administered to the normotensive rats , both the blood pressure and the heart rate were not significantly influenced by  
5 them.

It will be apparent from the Test Examples given above that the compounds of the present invention can exhibit effects as agents for treating or preventing functional diseases of digestive tracts, particularly intestinal diseases such as irritable bowel syndrome.